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(54) Title: CONFORMATIONALLY RESTRICTED AROMATIC INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN AND METHOD			
(57) Abstract			
<p>Novel compounds are provided which are inhibitors of MTP and thus are useful for lowering serum lipids and treating atherosclerosis and related diseases, and have the structure (I) or (IA) or (IB) including pharmaceutically acceptable salts thereof or prodrug esters thereof, wherein q is 0, 1 or 2; R^x is H, alkyl, aryl or halogen; A is (1) a bond; (2) -O-; or (3) (i); B is: (ii) or (iii) or (iv) or (v) (wherein (a = 2, 3 or 4)) or (vi) or (vii) or (viii); and wherein L², L¹, R¹, R², R³, R^{3'}, R^{3a}, R^{3b}, R⁴, R^{4'}, R⁵, X, (ix), (x) and (xi) are as defined herein.</p>			

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CONFORMATIONALLY RESTRICTED AROMATIC INHIBITORS OF
MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN AND METHOD

Field of the Invention

5 This invention relates to novel
conformationally restricted aromatic compounds
which inhibit microsomal triglyceride transfer
protein, and to methods for decreasing serum lipids
and treating atherosclerosis employing such
10 compounds.

Background of the Invention

 The microsomal triglyceride transfer
protein (MTP) catalyzes the transport of
15 triglyceride (TG), cholesteryl ester (CE), and
phosphatidylcholine (PC) between small unilamellar
vesicles (SUV). Wetterau & Zilversmit, Chem. Phys.
Lipids 38, 205-22 (1985). When transfer rates are
expressed as the percent of the donor lipid
20 transferred per time, MTP expresses a distinct
preference for neutral lipid transport (TG and CE),
relative to phospholipid transport. The protein
from bovine liver has been isolated and
characterized. Wetterau & Zilversmit, Chem. Phys.
25 Lipids 38, 205-22 (1985). Polyacrylamide gel
electrophoresis (PAGE) analysis of the purified
protein suggests that the transfer protein is a
complex of two subunits of apparent molecular
weights 58,000 and 88,000, since a single band was
30 present when purified MTP was electrophoresed under
nondenaturing condition, while two bands of
apparent molecular weights 58,000 and 88,000 were

identified when electrophoresis was performed in the presence of sodium dodecyl sulfate (SDS). These two polypeptides are hereinafter referred to as 58 kDa and 88 kDa, respectively, or the 58 kDa and the 88 kDa component of MTP, respectively, or the low molecular weight subunit and the high molecular weight subunit of MTP, respectively.

Characterization of the 58,000 molecular weight component of bovine MTP indicates that it is the previously characterized multifunctional protein, protein disulfide isomerase (PDI). Wetterau *et al.*, *J. Biol. Chem.* 265, 9800-7 (1990). The presence of PDI in the transfer protein is supported by evidence showing that (1) the amino terminal 25 amino acids of the bovine 58,000 kDa component of MTP is identical to that of bovine PDI, and (2) disulfide isomerase activity was expressed by bovine MTP following the dissociation of the 58 kDa - 88 kDa protein complex. In addition, antibodies raised against bovine PDI, a protein which by itself has no TG transfer activity, were able to immunoprecipitate bovine TG transfer activity from a solution containing purified bovine MTP.

PDI normally plays a role in the folding and assembly of newly synthesized disulfide bonded proteins within the lumen of the endoplasmic reticulum. Bulleid & Freedman, *Nature* 335, 649-51 (1988). It catalyzes the proper pairing of cysteine residues into disulfide bonds, thus catalyzing the proper folding of disulfide bonded proteins. In addition, PDI has been reported to be identical to the beta subunit of human prolyl 4-hydroxylase. Koivu *et al.*, *J. Biol. Chem.* 262, 6447-9 (1987). The role of PDI in the bovine transfer protein is not clear. It does appear to be an essential component of the transfer protein

as dissociation of PDI from the 88 kDa component of bovine MTP by either low concentrations of a denaturant (guanidine HCl), a chaotropic agent (sodium perchlorate), or a nondenaturing detergent (octyl glucoside) results in a loss of transfer activity. Wetterau et al., Biochemistry 30, 9728-35 (1991). Isolated bovine PDI has no apparent lipid transfer activity, suggesting that either the 88 kDa polypeptide is the transfer protein or that it confers transfer activity to the protein complex.

The tissue and subcellular distribution of MTP activity in rats has been investigated. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). Lipid transfer activity was found in liver and intestine. Little or no transfer activity was found in plasma, brain, heart, or kidney. Within the liver, MTP was a soluble protein located within the lumen of the microsomal fraction. Approximately equal concentrations were found in the smooth and rough microsomes.

Abetalipoproteinemia is an autosomal recessive disease characterized by a virtual absence of plasma lipoproteins which contain apolipoprotein B (apoB). Kane & Havel in The Metabolic Basis of Inherited Disease, Sixth edition, 1139-64 (1989). Plasma TG levels may be as low as a few mg/dL, and they fail to rise after fat ingestion. Plasma cholesterol levels are often only 20-45 mg/dL. These abnormalities are the result of a genetic defect in the assembly and/or secretion of very low density lipoproteins (VLDL) in the liver and chylomicrons in the intestine. The molecular basis for this defect has not been previously determined. In subjects examined, triglyceride, phospholipid, and cholesterol synthesis appear normal. At autopsy, subjects are

free of atherosclerosis. Schaefer et al., Clin. Chem. 34, B9-12 (1988). A link between the apoB gene and abetalipoproteinemia has been excluded in several families. Talmud et al., J. Clin. Invest. 82, 1803-6 (1988) and Huang et al., Am. J. Hum. Genet. 46, 1141-8 (1990).

Subjects with abetalipoproteinemia are afflicted with numerous maladies. Kane & Havel, supra. Subjects have fat malabsorption and TG accumulation in their enterocytes and hepatocytes. Due to the absence of TG-rich plasma lipoproteins, there is a defect in the transport of fat-soluble vitamins such as vitamin E. This results in acanthocytosis of erythrocytes, spinocerebellar ataxia with degeneration of the fasciculus cuneatus and gracilis, peripheral neuropathy, degenerative pigmentary retinopathy, and ceroid myopathy. Treatment of abetalipoproteinemic subjects includes dietary restriction of fat intake and dietary supplementation with vitamins A, E and K.

In vitro, MTP catalyzes the transport of lipid molecules between phospholipid membranes. Presumably, it plays a similar role in vivo, and thus plays some role in lipid metabolism. The subcellular (lumen of the microsomal fraction) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in the assembly of plasma lipoproteins, as these are the sites of plasma lipoprotein assembly. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). The ability of MTP to catalyze the transport of TG between membranes is consistent with this hypothesis, and suggests that MTP may catalyze the transport of TG from its site of synthesis in the endoplasmic reticulum (ER) membrane to nascent lipoprotein particles within the lumen of the ER.

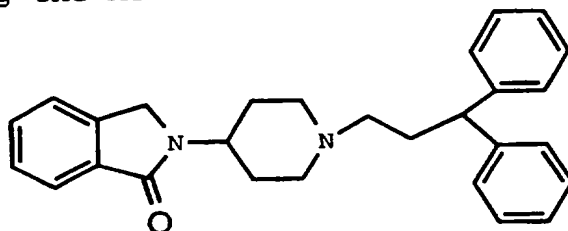
Olofsson and colleagues have studied lipoprotein assembly in HepG2 cells. Bostrom et al., J. Biol. Chem. 263, 4434-42 (1988). Their results suggest small precursor lipoproteins become
5 larger with time. This would be consistent with the addition or transfer of lipid molecules to nascent lipoproteins as they are assembled. MTP may play a role in this process. In support of this hypothesis, Howell and Palade, J. Cell Biol.
10 92, 833-45 (1982), isolated nascent lipoproteins from the hepatic Golgi fraction of rat liver. There was a spectrum of sizes of particles present with varying lipid and protein compositions. Particles of high density lipoprotein (HDL)
15 density, yet containing apoB, were found. Higgins and Hutson, J. Lipid Res. 25, 1295-1305 (1984), reported lipoproteins isolated from Golgi were consistently larger than those from the endoplasmic reticulum, again suggesting the assembly of
20 lipoproteins is a progressive event. However, there is no direct evidence in the prior art demonstrating that MTP plays a role in lipid metabolism or the assembly of plasma lipoprotein.

Recent reports (Science, Vol. 258, page
25 999, 1992; D. Sharp et al, Nature, Vol. 365, page 65, 1993) demonstrate that the defect causing abetalipoproteinemia is in the MTP gene, and as a result, the MTP protein. Individuals with abetalipoproteinemia have no MTP activity, as a
30 result of mutations in the MTP gene, some of which have been characterized. These results indicate that MTP is required for the synthesis of apoB containing lipoproteins, such as VLDL, the precursor to LDL. It therefore follows that
35 inhibitors of MTP would inhibit the synthesis of VLDL and LDL, thereby lowering VLDL levels, LDL

levels, cholesterol levels, and triglyceride levels in animals and man.

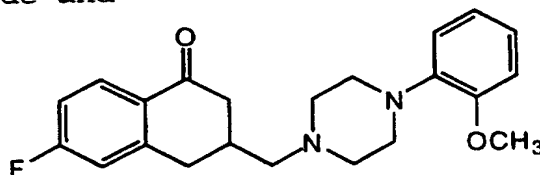
Canadian Patent Application No. 2,091,102 published March 2, 1994 (corresponding to U.S.

- 5 application Serial No. 117,362, filed September 3, 1993 (file DC21b)) which is incorporated herein by reference), reports MTP inhibitors which also block the production of apoB containing lipoproteins in a human hepatic cell line (HepG2 cells). This
 10 provides further support for the proposal that an MTP inhibitor would lower apoB containing lipoprotein and lipid levels in vivo. This Canadian patent application discloses a method for identifying the MTP inhibitors



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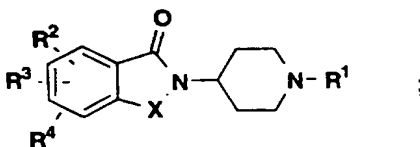
which has the name 2-[1-(3,3-diphenylpropyl)-4-piperidyl]-2,3-dihydro-3-oxo-1H-isoindole hydrochloride and



- 20 which has the name 1-[3-(6-fluoro-1-tetralanyl)-methyl]-4-O-methoxyphenyl piperazine.

EP 0643057A1 published March 15, 1995, discloses MTP inhibitors of the structure

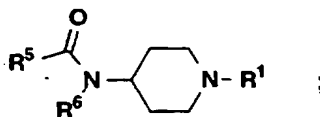
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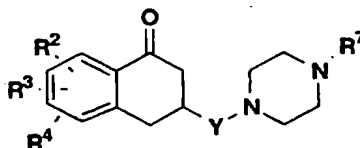
or

II



or

III



5

where X is: CHR^8 , $\begin{array}{c} -\text{CH}-\text{CH}- \\ | \quad | \\ \text{R}^9 \quad \text{R}^{10} \end{array}$ or $\begin{array}{c} -\text{C}=\text{C}- \\ | \quad | \\ \text{R}^9 \quad \text{R}^{10} \end{array}$;

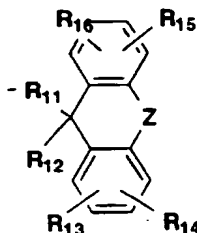
R^8 , R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

Y is $-(\text{CH}_2)_m-$ or $\begin{array}{c} -\text{C}- \\ || \\ \text{O} \end{array}$

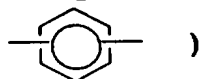
where m is 2 or 3;

R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl has at least 2 carbons), diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl (wherein alkyl has at least 2 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl has at least 2 carbons); all of the aforementioned R^1 groups being optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo; or

R^1 is a group of the structure

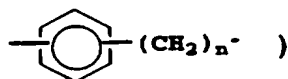


R¹¹ is a bond, alkylene, alkenylene or alkynylene of up to 6 carbon atoms, arylene (for example



5

or mixed arylene-alkylene (for example



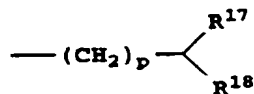
10 where n is 1 to 6;

R¹² is hydrogen, alkyl, alkenyl, aryl, heteroaryl, haloalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy, heteroarylalkyl or cycloalkylalkyl;

15 Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

R¹³, R¹⁴, R¹⁵, and R¹⁶ are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, carboxy, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

25 or R¹ is

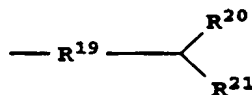


wherein p is 1 to 8 and R¹⁷ and R¹⁸ are each independently H, alkyl, alkenyl, aryl, arylalkyl,

30 heteroaryl, heteroarylalkyl, cycloalkyl or

cycloalkylalkyl, at least one of R¹⁷ and R¹⁸ being other than H;

or R¹ is



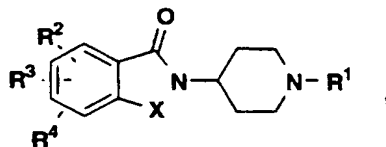
- 5 wherein R¹⁹ is aryl or heteroaryl;
 R²⁰ is aryl or heteroaryl;
 R²¹ is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or
 10 cycloalkylalkoxy;
 R², R³, R⁴ are independently hydrogen, halo, alkyl, haloalkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl,
 15 hydroxy or haloalkyl;
 R⁵ is alkyl of at least 2 carbons, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, polycycloalkenyl,
 20 polycycloalkenylalkyl, heteroarylcarbonyl, all of the R⁵ and R⁶ substituents being optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl,
 25 cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxy, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy,
 30 hydroxy, nitro, cyano, amino, substituted amino (wherein the amino includes 1 or 2 substituents which are alkyl, or aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl,
 35 alkylcarbonyl, arylcarbonyl, arylaminocarbonyl,

- alkoxycarbonyl, aminocarbonyl,
alkynylaminocarbonyl, alkylamino-carbonyl,
alkenylaminocarbonyl, alkylcarbonyloxy,
arylcarbonyloxy, alkylcarbonylamino, arylcarbonyl-
5 amino, arylsulfinyl, arylsulfinylalkyl,
arylsulfonyl, alkylsulfonyl, arylsulfonylamino;
with the proviso that when R^5 is CH_3 , R^6 is not H;
and where R^5 is phenyl, the phenyl preferably
includes an ortho hydrophobic substituent such as
10 alkyl, haloalkyl, aryl, aryloxy or arylalkyl;
 R^6 is hydrogen or C_1 - C_4 alkyl or C_1 - C_4
alkenyl;
 R^7 is alkyl, aryl or arylalkyl wherein
alkyl or the alkyl portion is optionally
15 substituted with oxo; and
including pharmaceutically acceptable salts
and anions thereof.

In the formula I compounds, where X is CH₂ and R², R³ and R⁴ are each H, R¹ will be other than 3,3-diphenylpropyl.

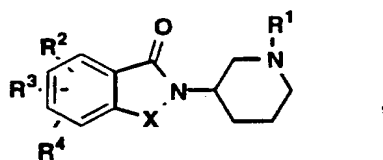
In the formula III compounds, where one of R², R³ and R⁴ is 6-fluoro, and the others are H, R⁷ will be other than 4-O-methoxyphenyl.

U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e) discloses compounds of the structure

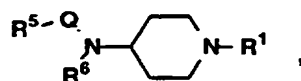


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or

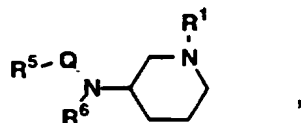


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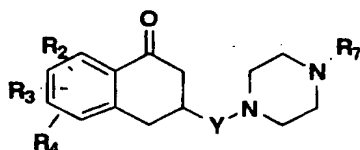


15

or



or



where Q is $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$ or $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{S}}}\text{—}$;

X is: CHR^8 , $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$, $\text{—}\underset{\text{R}^9}{\text{CH}}\text{—}\underset{\text{R}^{10}}{\text{CH}}\text{—}$ or $\text{—}\underset{\text{R}^9}{\text{C}}=\underset{\text{R}^{10}}{\text{C}}\text{—}$;

R^8 , R^9 and R^{10} are independently hydrogen, alkyl,
 5 alkenyl, alkynyl, aryl, arylalkyl, heteroaryl,
 heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

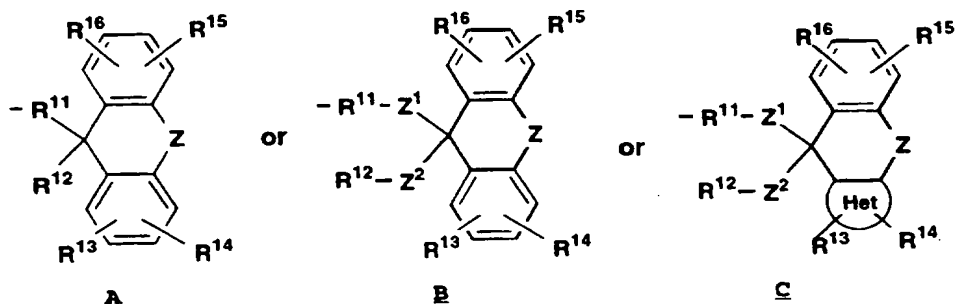
Y is $\text{—}(\text{CH}_2)_m\text{—}$ or $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$

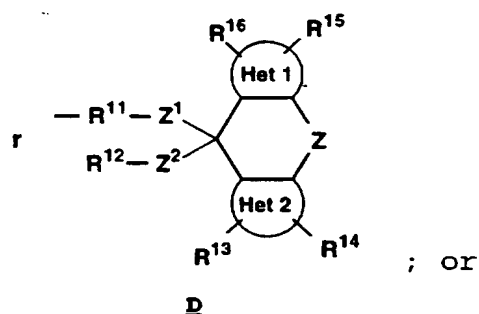
wherein m is 2 or 3;

10 R^1 is alkyl, alkenyl, alkynyl, aryl,
 heteroaryl, arylalkyl wherein alkyl has at least 2
 carbons, diarylalkyl, arylalkenyl, diarylalkenyl,
 arylalkynyl, diarylalkynyl, diarylalkylaryl,
 heteroarylalkyl wherein alkyl has at least 2
 15 carbons, cycloalkyl, or cycloalkylalkyl wherein
 alkyl has at least 2 carbons, all optionally
 substituted through available carbon atoms with 1,
 2, 3 or 4 groups selected from halo, haloalkyl,
 alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl,
 20 alkylmercapto, arylmercapto, cycloalkyl, cyclo-
 alkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl,
 hydroxy or oxo;

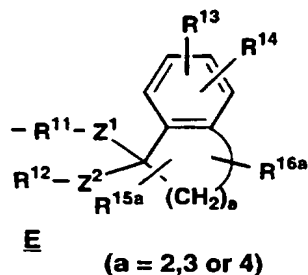
or R^1 is a fluorenyl-type group of the
 structure

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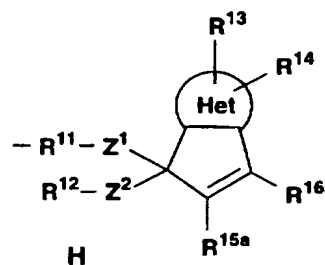
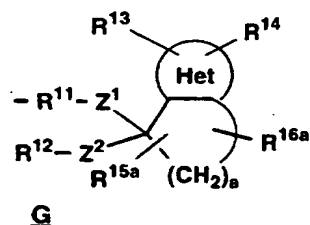
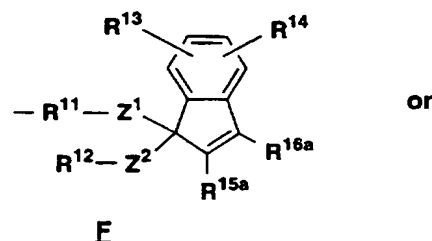




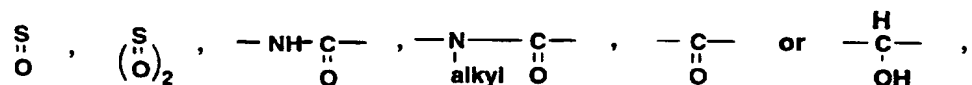
R^1 is an indenyl-type group of the structure



(a = 2,3 or 4)



Z^1 and Z^2 are the same or different and are independently a bond, O, S,



with the proviso that with respect to **E**, at least one of Z^1 and Z^2 will be other than a bond; R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene; R^{12} is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos that

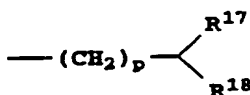
(1) when R^{12} is H, aryloxy, alkoxy or
 arylalkoxy, then Z^2 is $-\text{NH}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$, $-\underset{\text{alkyl}}{\text{N}}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$, $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$
 or a bond and

(2) when Z^2 is a bond, R^{12} cannot be
 5 heteroaryl or heteroarylalkyl;

Z is bond, O, S, N-alkyl, N-aryl, or
 alkylene or alkenylene from 1 to 5 carbon atoms;
 R^{13} , R^{14} , R^{15} , and R^{16} are independently hydrogen,
 alkyl, halo, haloalkyl, aryl, cycloalkyl, cyclo-
 10 heteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy,
 nitro, amino, thio, alkylsulfonyl, arylsulfonyl,
 alkylthio, arylthio, aminocarbonyl, alkylcarbon-
 yloxy, arylcarbonylamino, alkylcarbonylamino,
 arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

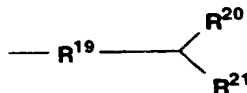
15 R^{15a} and R^{16a} are independently hydrogen,
 alkyl, halo, haloalkyl, aryl, cycloalkyl, cyclo-
 heteroalkyl, alkenyl, alkynyl, alkoxy, alkyl-
 sulfonyl, arylsulfonyl, alkylthio, arylthio, amino-
 carbonyl, alkylcarbonyloxy, arylcarbonylamino,
 20 alkylcarbonylamino, arylalkyl, heteroaryl,
 heteroarylalkyl, or aryloxy;

or R^1 is a group of the structure



25 wherein p is 1 to 8 and R^{17} and R^{18} are each
 independently H, alkyl, alkenyl, aryl, arylalkyl,
 heteroaryl, heteroarylalkyl, cycloalkyl or
 cycloalkylalkyl at least one of R^{17} and R^{18} being
 other than H;

30 or R^1 is a group of the structure



wherein R^{19} is aryl or heteroaryl;

R^{20} is aryl or heteroaryl;

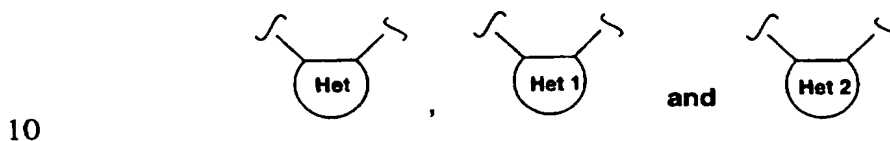
R²¹ is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

5 R², R³, R⁴ are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

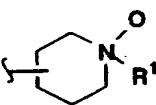
10 R⁵ is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkyl-alkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, 15 cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkyl-amino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through 20 selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxy-alkyl, arylalkoxy, arylazo, heteroaryloxo, hetero- 25 arylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, 30 arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, 35 arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfinyl;

R⁶ is hydrogen or C₁-C₄ alkyl or C₁-C₄ alkenyl; all optionally substituted with 1, 2, 3 or 4 groups which may independently be any of the substituents listed in the definition of R⁵ set out above;

R⁷ is alkyl, aryl or arylalkyl wherein alkyl by itself or as part of arylalkyl is optionally substituted with oxo $\left(\begin{array}{c} \text{O} \\ || \end{array} \right)$;



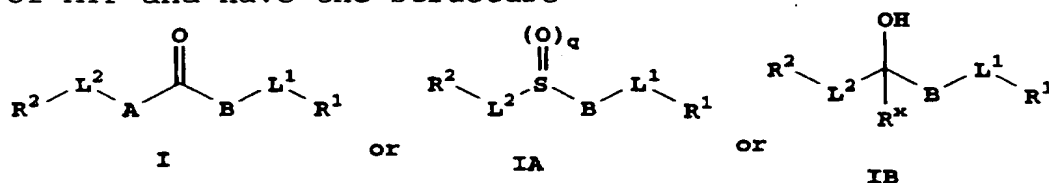
are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

15 N-oxides  thereof; and pharmaceutically acceptable salts thereof; with the provisos that where in the first formula X is CH₂, and R², R³ and R⁴ are each H, then R¹ will be other than 3,3-diphenylpropyl, and in the fifth formula, where one of R², R³ and R⁴ is 6-fluoro, and the others are H, R⁷ will be other than 4-(2-methoxyphenyl).

20

Summary of the Invention

In accordance with the present invention, novel compounds are provided which are inhibitors of MTP and have the structure



including pharmaceutically acceptable salts thereof, wherein q is 0, 1 or 2;

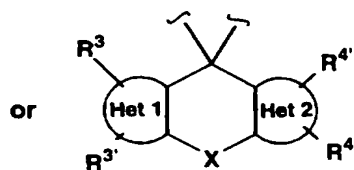
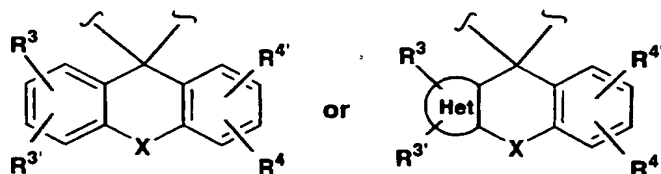
A is (1) a bond;

10 (2) -O- ; or



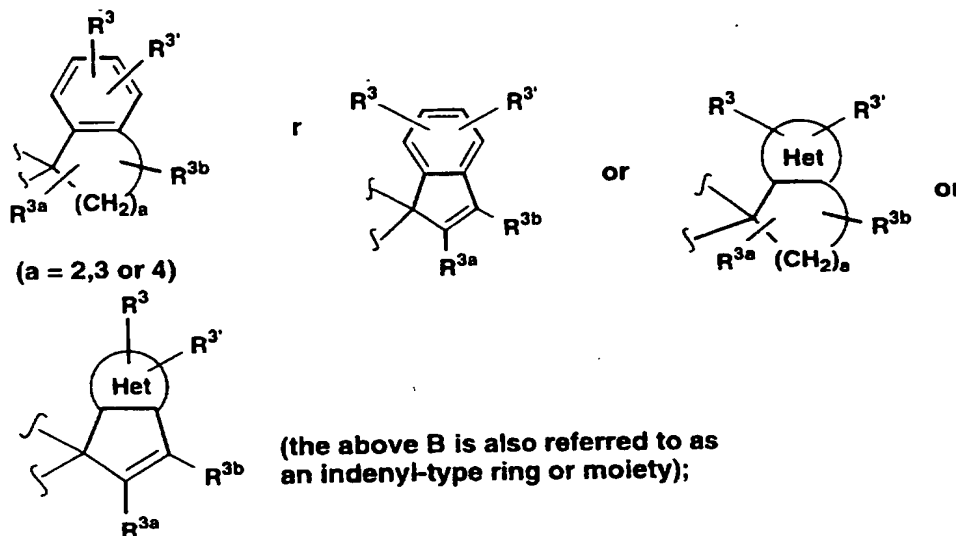
where R⁵ is H or lower alkyl or R⁵ together with R² forms a carbocyclic or heterocyclic ring system
15 containing 4 to 8 members in the ring.

B is a fluorenyl-type group of the structure:



(the above B is also referred to as a fluorenyl-type ring or moiety); or

B is an indenyl-type group of the structure



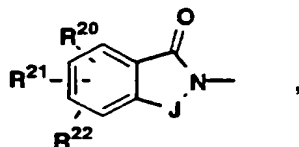
R^x is H, alkyl or aryl;

- R^1 is H, alkyl, alkenyl, alkynyl, alkoxyl, (alkyl or aryl)₃Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, substituted alkylamino, substituted arylalkylamino, aryl, aryl-alkyl, arylamino, aryloxy, cycloheteroalkyl, heteroaryl, heteroarylamino, heteroaryloxy, arylsulfonylamino, heteroarylsulfonylamino, arylthio, arylsulfinyl, arylsulfonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, $-PO(R^{13})(R^{14})$, (where R^{13} and R^{14} are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkyl-alkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy); R^1 can also be aminocarbonyl (where the amino may optionally be substituted with one or two aryl, alkyl or heteroaryl groups); cyano, 1,1-(alkoxyl or aryloxy)₂alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring, such as 1,3-dioxane or 1,3-dioxolane, connected to L^1 (or L^2 in the case of R^2) at the 2-position); 1,3-dioxane or

1,3-dioxolane connected to L^1 (or L^2 in the case of R^2) at the 4-position.

The R^1 group may have from one to four substituents, which can be any of the R^3 groups or R^1 groups, and any of the preferred R^1 substituents set out below.

R^1 may be substituted with the following preferred substituents: alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxy carbonylamino, aryloxy carbonyl-amino, heteroaryloxy carbonylamino, uriedo (where the uriedo nitrogens may be substituted with alkyl, aryl or heteroaryl), heterocyclylcarbonylamino (where the heterocycle is connected to the carbonyl group via a nitrogen or carbon atom), alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,



20

where J is: CHR^{23} , $\begin{array}{c} \text{---C---} \\ || \\ \text{O} \end{array}$, $\begin{array}{c} \text{---CH---CH---} \\ | \quad | \\ R^{24} \quad R^{25} \end{array}$ or $\begin{array}{c} \text{---C=C---} \\ | \quad | \\ R^{24} \quad R^{25} \end{array}$;

R^{23} , R^{24} and R^{25} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

R^{20} , R^{21} , R^{22} are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl; and these preferred substituents may either be directly attached to R^1 , or attached via an alkylene chain at an open position.

R^2 is the same or different from R^1 and is independently any of the groups set out for R^1 , H,

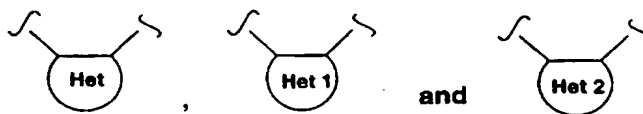
polyhaloalkyl (such as CF_3CH_2 , $\text{CF}_3\text{CF}_2\text{CH}_2$ or CF_3) or cycloheteroalkyl, and may be substituted with one to four of any of the groups defined for R^3 , or any of the substituents preferred for R^1 .

- 5 L^1 is a linking group containing from 1 to 10 carbons in a linear chain (including alkylene, alkenylene or alkynylene), which may contain, within the linking chain any of the following: one or two alkenes, one or two alkynes, an oxygen, an amino group optionally substituted with alkyl or aryl, an oxo group; and may be substituted with one to five alkyl or halo groups (preferably F).

- 10 L^2 may be the same or different from L^1 and may independently be any of the L^1 groups set out above or a single bond.

- 15 R^3 , $\text{R}^{3'}$, R^4 and $\text{R}^{4'}$ may be the same or different and are independently selected from H, halogen, CF_3 , haloalkyl, hydroxy, alkoxy, alkyl, aryl, alkenyl, alkenyloxy, alkynyl, alkynyloxy, alkanoyl, nitro, amino, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, cycloheteroalkyl, cycloheteroalkylalkyl, cyano, Ar, Ar-alkyl, ArO, Ar-amino, Ar-thio, Ar-sulfinyl, Ar-sulfonyl, Ar-carbonyl, Ar-carbonyloxy or Ar-carbonylamino, wherein Ar is aryl or heteroaryl and Ar may optionally include 1, 2 or 3 additional rings fused to Ar;

- 25 30 R^{3a} and R^{3b} are the same or different and are independently any of the R^3 groups except hydroxy, nitro, amino or thio;



are the same or different and independently represent a 5 or 6 membered heteroaryl ring which may contain 1, 2, 3 or 4 heteroatoms in the ring which are independently N, S or O; and including N-oxides.

X (in the fluorenyl type ring) is a bond, or is one of the following groups:

- (1) $\begin{array}{c} \text{---S---} \\ | \\ (\text{O})_{n'} \end{array}$
- (2) ---O---
- (3) $\begin{array}{c} \text{---N---} \\ | \\ \text{R}^6 \end{array}$
- (4) $\begin{array}{c} \text{---C---} \\ / \quad \backslash \\ \text{R}^7 \quad \text{R}^8 \end{array}$
- (5) $\begin{array}{c} \text{---C---C---} \\ / \quad \backslash \quad / \quad \backslash \\ \text{R}^9 \quad \text{R}^{10} \text{R}^{9'} \quad \text{R}^{10'} \end{array}$
- (6) $\begin{array}{c} \text{---C=C---} \\ | \quad | \\ \text{R}^{9''} \quad \text{R}^{10''} \end{array}$
- (7) $\begin{array}{c} \text{---C---Y---} \\ / \quad \backslash \\ \text{R}^9 \quad \text{R}^{10} \end{array}$

wherein

Y is O, N-R⁶ or S;

n' is 0, 1 or 2;

R⁶ is H, lower alkyl, aryl, -C(O)-R¹¹ or -C(O)-O-R¹¹;

R⁷ and R⁸ are the same or different and are independently H, alkyl, aryl, halogen, -O-R¹², or R⁷ and R⁸ together can be oxygen to form a ketone;

R⁹, R¹⁰, R^{9'} and R^{10'} are the same or different and are independently H, lower alkyl, aryl or -O-R¹¹;

R^{9''} and R^{10''} are the same or different and are independently H, lower alkyl, aryl, halogen or

-O-R¹¹;

R¹¹ is alkyl or aryl;

R¹² is H, alkyl or aryl.

The following provisos apply to formula I

5 compounds:

(a) when R¹ is unsubstituted alkyl or unsubstituted arylalkyl, L¹ cannot contain amino;

(b) when R¹ is alkyl, L¹ cannot contain amino and oxo in adjacent positions (to form an amido group);

(c) when R²L²A- is H₂N-, R¹L¹ cannot contain amino;

(d) when R¹ is cyano, L¹ must have more than 2 carbons;

(e) R¹L¹ must contain at least 3 carbons.

With respect to compounds of the invention IA and IB, R²L² cannot have an O or N atom directly attached to S=(O)_q or CR^x(OH), and for IA, R²L² cannot be H.

With respect to compounds of the invention I, IA and IB, where R¹ or R² is cycloheteroalkyl, R¹ or R² is exclusive of 1-piperidinyl, 1-pyrrolidinyl, 1-azetidinyll or 1-(2-oxo-pyrrolidinyl).

The pharmaceutically acceptable salts of the compounds of formulae I, IA and IB include alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium, as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, ethylenediamine, t-butylamine, t-octylamine, dehydroabietylamine, as well as pharmaceutically acceptable anions such as chloride, bromide, iodide, tartrate, acetate, methanesulfonate, maleate, succinate, glutarate, and salts of naturally occurring amino acids such

as arginine, lysine, alanine and the like, and prodrug esters thereof.

In addition, in accordance with the present invention, a method for preventing, inhibiting or
5 treating atherosclerosis, pancreatitis or obesity is provided, wherein a compound of formula I, IA or IB as defined hereinbefore (and including compounds excluded by provisos (a), (b), (c), (d) and (e) set out hereinbefore) is administered in an amount
10 which decreases the activity of microsomal triglyceride transfer protein.

Furthermore, in accordance with the present invention, a method is provided for lowering serum lipid levels, cholesterol and/or triglycerides, or
15 inhibiting and/or treating hyperlipemia, hyperlipid-emia, hyperlipoproteinemia, hypercholesterolemia hypertriglyceridemia and/or hyperglycemia, non-insulin dependent diabetes (Type II diabetes), wherein a compound of formula I, IA
20 or IB as defined hereinbefore (and including compounds excluded by provisos (a), (b), (c), (d) and (e) set out hereinbefore) is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

25

Detailed Description of the Invention

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

30 The term "MTP" refers to a polypeptide or protein complex that (1) if obtained from an organism (e. g., cows, humans, etc.), can be isolated from the microsomal fraction of homogenized tissue; and (2) stimulates the
35 transport of triglycerides, cholesterol esters, or phospholipids from synthetic phospholipid vesicles, membranes or lipoproteins to synthetic vesicles,

membranes, or lipoproteins and which is distinct from the cholesterol ester transfer protein [Drayna et al., Nature 327, 632-634 (1987)] which may have similar catalytic properties.

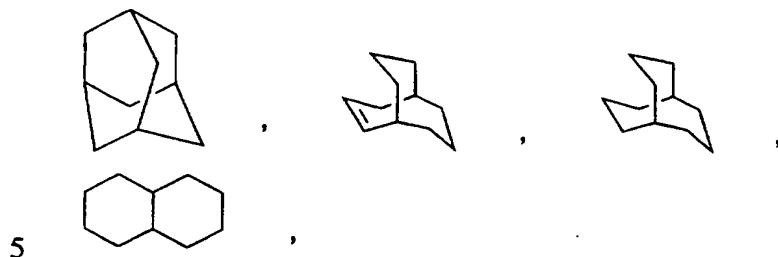
- 5 The phrase "stabilizing" atherosclerosis as used in the present application refers to slowing down the development of and/or inhibiting the formation of new atherosclerotic lesions.

- The phrase "causing the regression of"
10 atherosclerosis as used in the present application refers to reducing and/or eliminating atherosclerotic lesions.

- Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone
15 or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, more preferably 1 to 12 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl,
20 butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4
25 substituents which may be any of the R^3 groups, or the R^1 substituents set out herein.

- Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially
30 unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocycloalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 12
35 carbons, forming the ring and which may be fused to 1 aromatic ring as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl,

cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted with 1 to 4 substituents which may be any of the R^3 groups, or the R^1 substituents set out herein.

10 The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 5 to 20 carbons, preferably 6 to 12 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexa-
15 dienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

The term "polycycloalkyl" as employed herein alone or as part of another group refers to a bridged multicyclic group containing 5 to 20
20 carbons and containing 0 to 3 bridges, preferably 6 to 12 carbons and 1 or 2 bridges. Exemplary polycycloalkyl groups include [3.3.0]-bicyclooctanyl, adamantanyl, [2.2.1]-bicycloheptanyl, [2.2.2]-bicyclooctanyl and the
25 like and may be optionally substituted as defined for cycloalkyl.

The term "polycycloalkenyl" as employed herein alone or as part of another group refers to a bridged multicyclic group containing 5 to 20
30 carbons and containing 0 to 3 bridges and containing 1 or 2 double bonds, preferably 6 to 12 carbons and 1 or 2 bridges. Exemplary polycycloalkyl groups include [3.3.0]-bicyclooctenyl, [2.2.1]-bicycloheptenyl, [2.2.2]-

bicyclooctenyl and the like and may be optionally substituted as defined for cycloalkyl.

The term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl) and may optionally include one to three additional rings fused to Ar (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cyclo-alkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, hetero-aryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, hetero-arylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkyl-aminocarbonyl, arylaminocarbonyl, alkoxy carbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfon-aminocarbonyl or any of the R³ groups, or the R¹ substituents set out herein.

The term "aralkyl", "aryl-alkyl" or "aryllower alkyl" as used herein alone or as part of another group refers to alkyl groups as discussed above having an aryl substituent, such as benzyl or phenethyl, or naphthylpropyl, or an aryl as defined above.

The term "lower alkoxy", "alkoxy",
"aryloxy" or "aralkoxy" as employed herein alone or
as part of another group includes any of the above
alkyl, aralkyl or aryl groups linked to an oxygen
5 atom.

The term "amino" as employed herein alone
or as part of another group may optionally be
substituted with one or two substituents such as
alkyl, aryl, arylalkyl, heteroaryl,
10 heteroarylalkyl, cycloheteroalkyl,
cycloheteroalkylalkyl and/or cycloalkyl.

The term "lower alkylthio", "alkylthio",
"arylthio" or "aralkylthio" as employed herein
alone or as part of another group includes any of
15 the above alkyl, aralkyl or aryl groups linked to a
sulfur atom.

The term "lower alkylamino", "alkylamino",
"arylamino", or "arylalkylamino" as employed herein
alone or as part of another group includes any of
20 the above alkyl, aryl or arylalkyl groups linked to
a nitrogen atom.

The term "acyl" as employed herein by
itself or part of another group, as defined herein,
refers to an organic radical linked to a carbonyl
25 $\left(\begin{array}{c} \text{O} \\ \parallel \\ \text{C} \end{array} \right)$ group; examples of acyl groups include
alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl,
cycloal-kanoyl, and the like.

The term "alkanoyl" as used herein alone or
as part of another group refers to alkyl linked to
30 a carbonyl group.

Unless otherwise indicated, the term "lower
alkenyl" or "alkenyl" as used herein by itself or
as part of another group refers to straight or
branched chain radicals of 2 to 20 carbons,
35 preferably 3 to 12 carbons, and more preferably 1
to 8 carbons in the normal chain, which include one
to six double bonds in the normal chain, such as

vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 5 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, 10 cyclohetero-alkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, alkylthio or any of the R³ groups, or the R¹ substituents set out herein.

Unless otherwise indicated, the term "lower 15 alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one 20 triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like, and 25 which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, 30 arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, or any of the R³ groups, or the R¹ substituents set out herein.

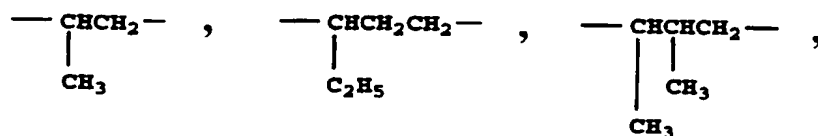
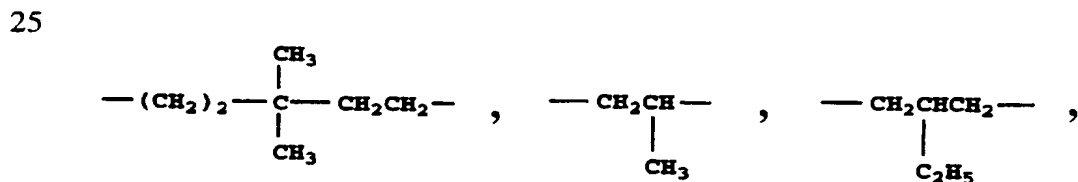
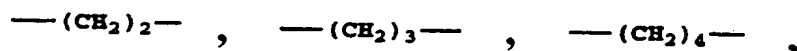
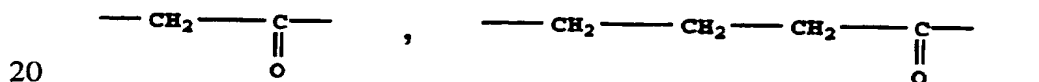
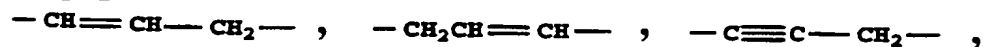
The term "alkylene" as employed herein alone or as part of another group refers to alkyl 35 groups as defined above having single bonds for attachment to other groups at two different carbon

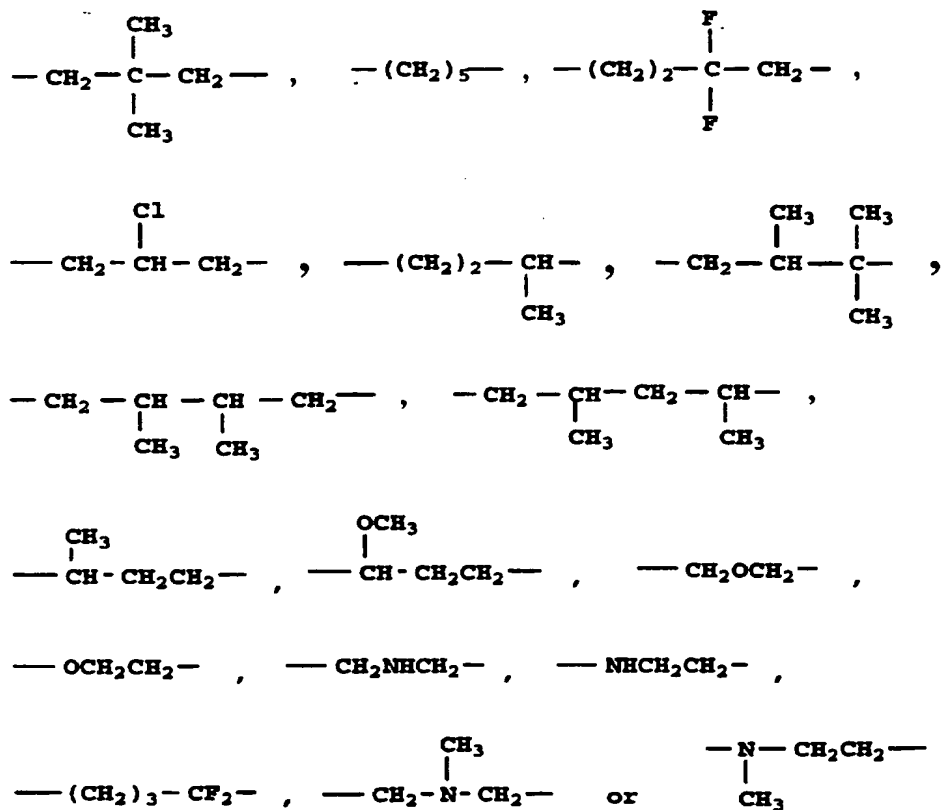
atoms and may optionally be substituted as defined above for "alkyl".

Ther terms "alkenylene" and "alkynylene" as employed herein alone or as part of another group refer to alkenyl groups as defined above and alkynyl groups as defined above, respectively, having single bonds for attachment at two different carbon atoms.

Suitable alkylene, alkenylene or alkynylene groups or $(CH_2)_m$, $(CH_2)_n$ or $(CH_2)_p$ (which may include alkylene, alkenylene or alkynylene groups) as defined herein, may optionally include 1, 2, or 3 substituents which include any of the R^3 groups, or the R^1 substituents set out herein.

Examples of alkylene, alkenylene and alkynylene include





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The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF₃, with chlorine or fluorine being preferred.

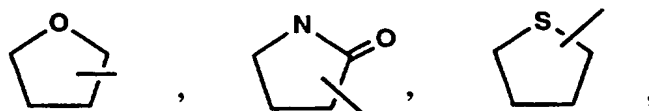
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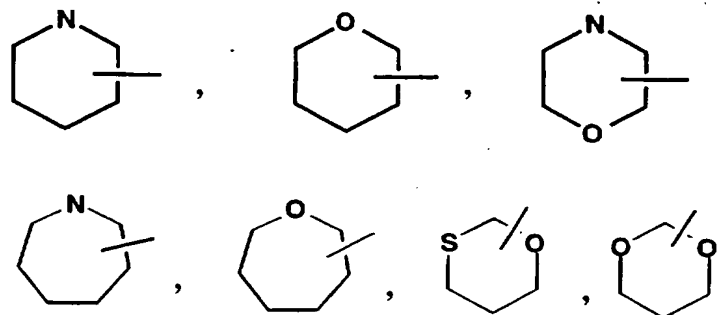
The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

20

The term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker (CH₂)_p (which is defined above), such as

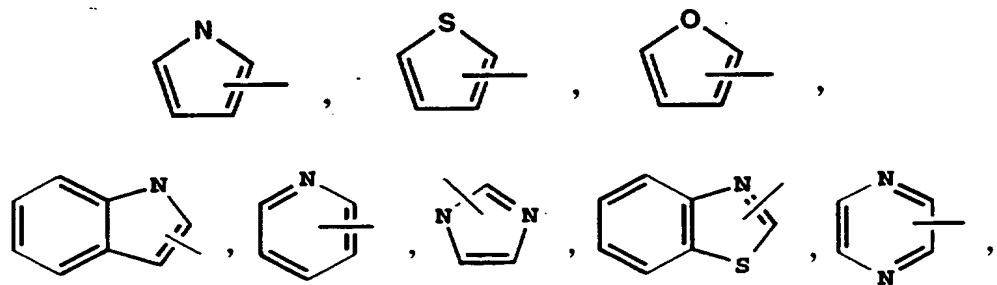
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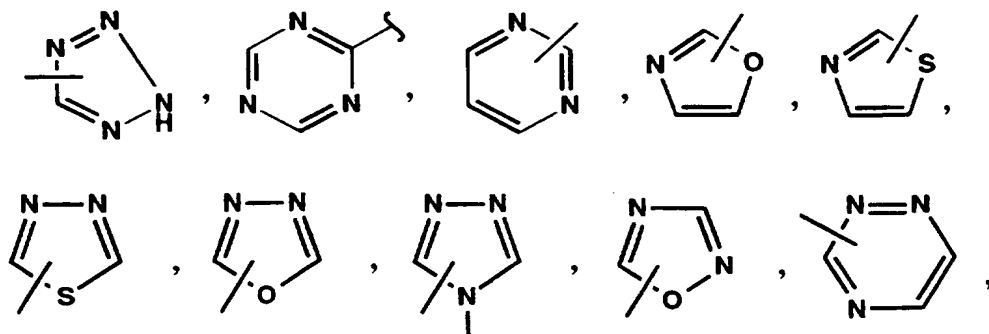


- 5 and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of of the R^3 groups, or the R^1 substituents set out herein. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or
 10 cycloheteroalkyl ring.

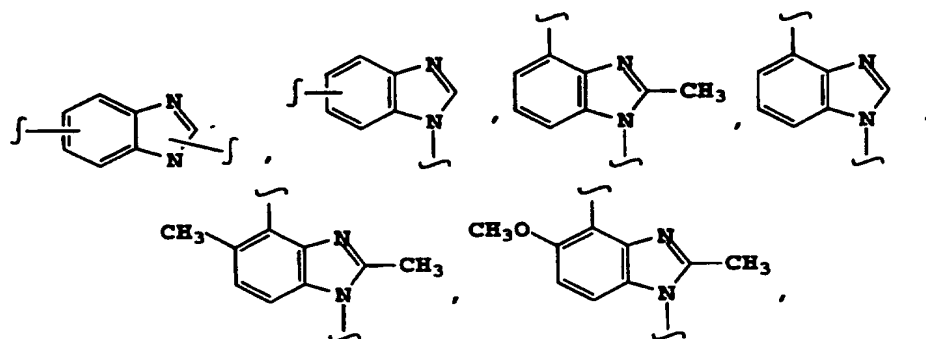
The term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6-membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and
 15 such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides, such as



5



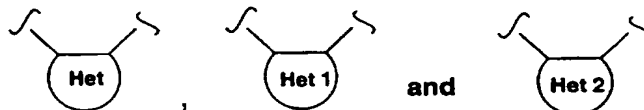
10



and the like.

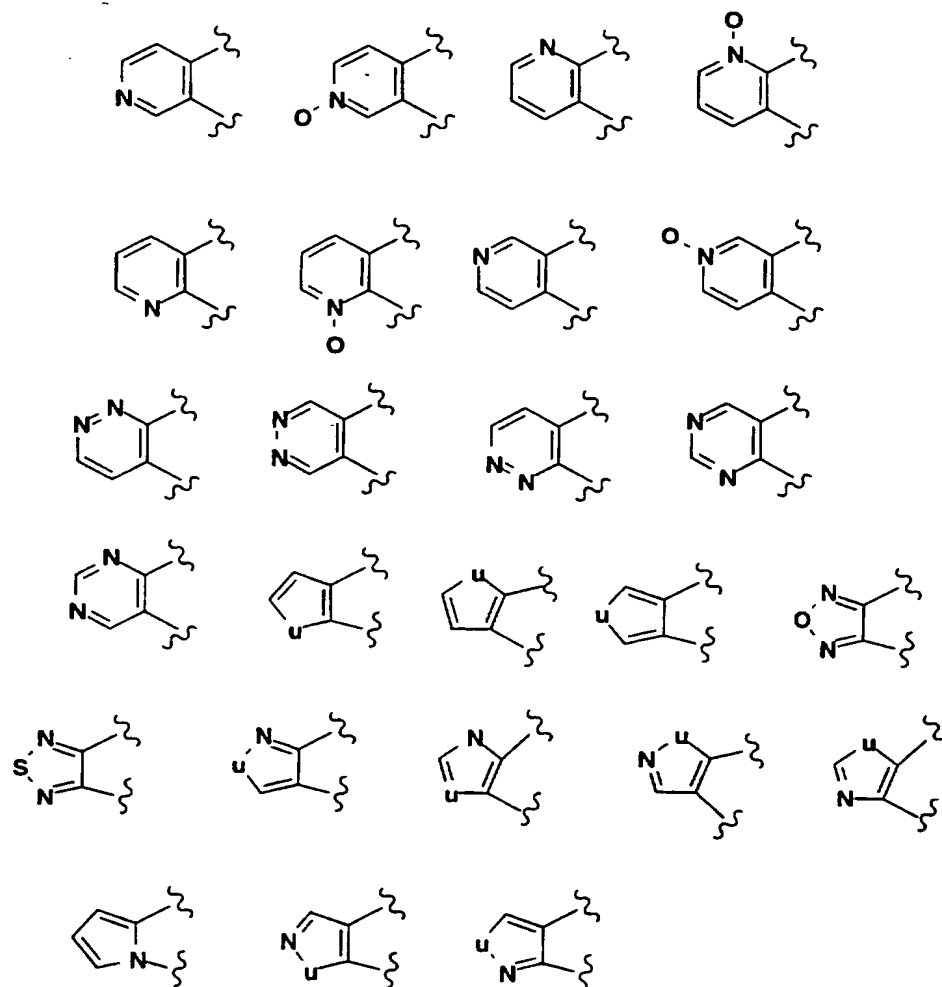
Ar may be either aryl or heteroaryl as defined above.

15



are the same or different, as defined hereinbefore, and are attached to the central ring of the indenyl or fluorenyl type group at adjacent positions (that is, ortho or 1,2-positions). Examples of such groups include

20



wherein u is selected from O, S, and NR^{7a} ;
 R^{7a} is H, lower alkyl, aryl, $-\text{C}(\text{O})\text{R}^{7b}$, $-\text{C}(\text{O})\text{OR}^{7b}$;
 R^{7b} is alkyl or aryl.

- 5 The heteroaryl groups including the above groups may optionally include 1 to 4 substituents such as any of the R^3 groups, or the R^1 substituents set out herein. In addition, any of the above rings can be fused to a cycloalkyl, aryl,
 10 heteroaryl or cycloheteroalkyl ring.

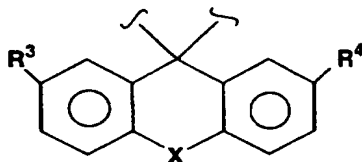
The term "cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(\text{CH}_2)_p$ chain.

- 15 The term "heteroarylalkyl" or "heteroaryl-alkenyl" as used herein alone or as part of another

group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(CH_2)_p$ -chain, alkylene or alkenylene as defined above.

The term "polyhaloalkyl" as used herein
 5 refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2 , CF_3 or $CF_3CF_2CH_2$.

Preferred are compounds of formula I
 10 wherein A is NH,
 B is



X is a bond, oxygen or sulfur; R^3 and R^4 are independently H or F.

15 Preferred R^1 groups are aryl, preferably phenyl, heteroaryl, preferably imidazolyl, benzimidazolyl, indolyl, or pyridyl (preferably substituted with one of the preferred R^1 substituents: arylcarbonylamino,
 20 heteroarylcarbonyl-amino, cycloalkylcarbonylamino, alkoxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroaryl-sulfonylamino), $PO(OAlkyl)_2$, heteroarylthio, benzthiazole-2-thio, imidazole-2-thio, alkyl, or alkenyl, cycloalkyl
 25 such as cyclohexyl, or 1,3-dioxan-2-yl.

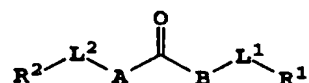
Preferred R^2 groups are alkyl, polyfluoroalkyl (such as 1,1,1-trifluoroethyl), alkenyl, aryl or heteroaryl (preferably substituted with one of the preferred R^1 substituents above),
 30 or $PO(OAlkyl)_2$.

If R^2 is alkyl, 1,1,1-trifluoroethyl, or alkenyl, it is preferred that R^1 is other than alkyl or alkenyl.

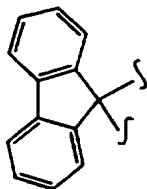
It is preferred that L^1 contains 1 to 5 atoms in the linear chain and L^2 is a bond or lower alkylene.

- Preferred embodiments of formula IA and
 5 formula IB compounds of the invention include those where B, L^1 , L^2 , R^1 and R^2 are as set out with respect to the preferred embodiments of the formula I compounds, q is 0 or 2 and R^x is H.

- Also preferred are compounds of the
 10 structure

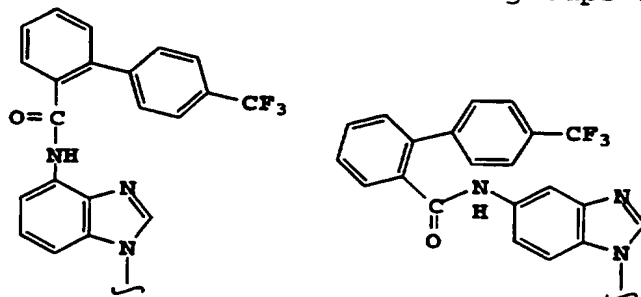


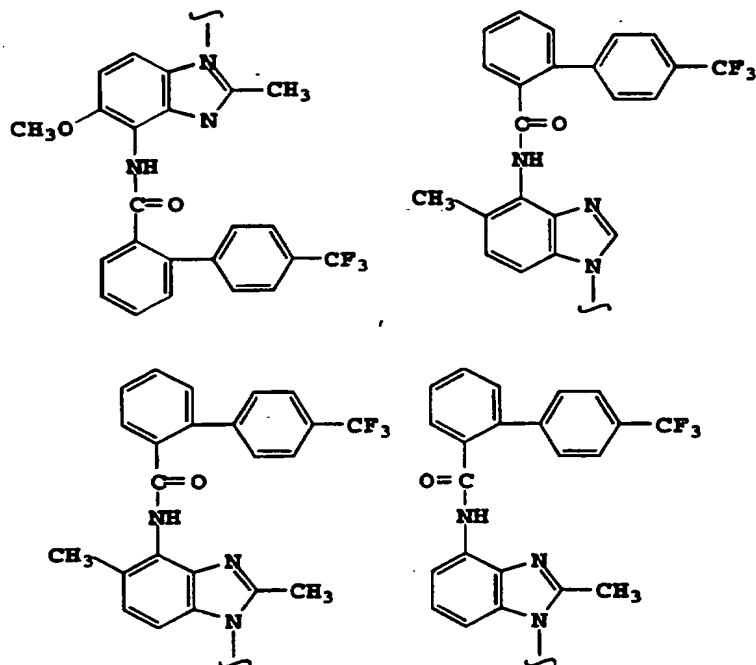
where B is



A is NH,

- 15 L^2 is a bond,
 R^2 is CF_3CH_2 ,
 L^1 is $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$, and
 R^1 is heteroaryl which is a 5-membered aromatic ring which includes 2 nitrogens, which
 20 ring is fused to an aryl ring and is substituted on the aryl moiety. Examples of preferred R^1 groups include substituted benzimidazole groups including



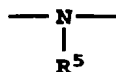
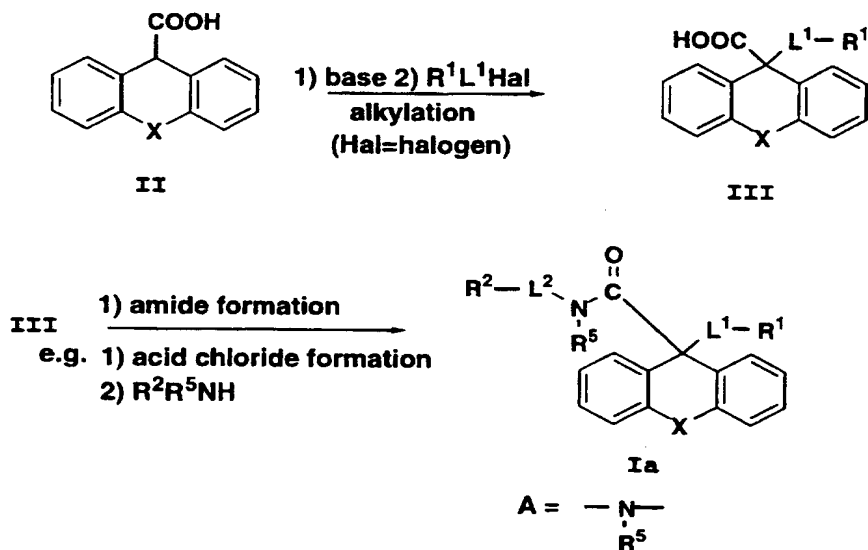
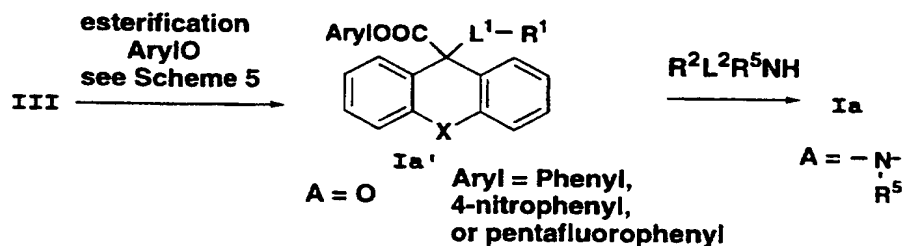


5 The compounds of formulae I, IA and IB may be prepared by the exemplary processes described in the following reaction schemes. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples.

10

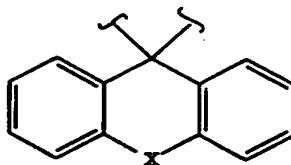
Reaction Scheme 1 (Amides)

Preparation of Compounds of Formula I where A is

5 Scheme 1AScheme 1B

10

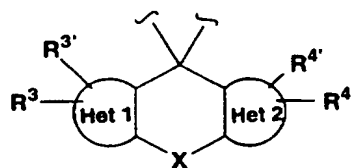
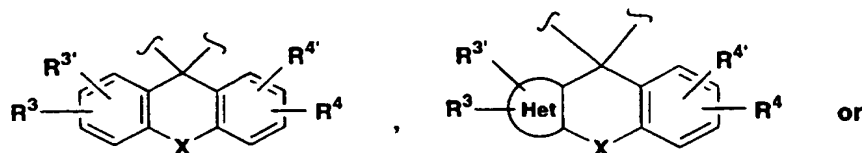
It will be appreciated that in the above reactions and the reactions to follow, unless otherwise indicated, the moiety "B" in the starting materials, intermediates and final products is set out as



for purposes of illustration only.

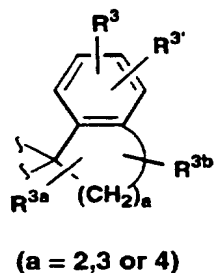
It will be appreciated that the "B" moiety in the starting materials, intermediates and final products in all reactions set forth herein, unless indicated to the contrary may be any of the

5 fluorenyl-type groups

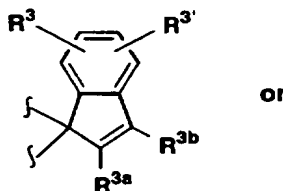


as well as any of indenyl-type

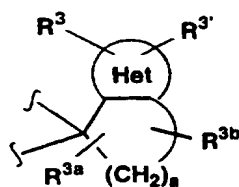
10 groups



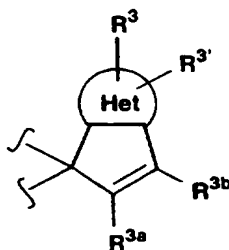
or



or



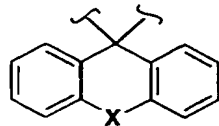
or



15 The above B moieties (including all fluorenyl-type groups and all indenyl-type groups) are collectively referred to as "fluorenyl-type" moieties. The use of the first fluorenyl-type group (as set out in the previous paragraph) in the

20 Reaction Schemes is for purposes of illustration only; any of the 3 fluorenyl groups or 4 indenyl

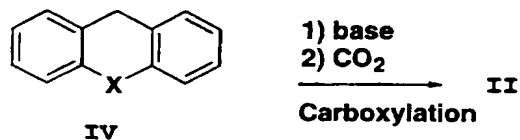
groups as set out above may be employed in any of the Reaction Schemes set out herein in place of



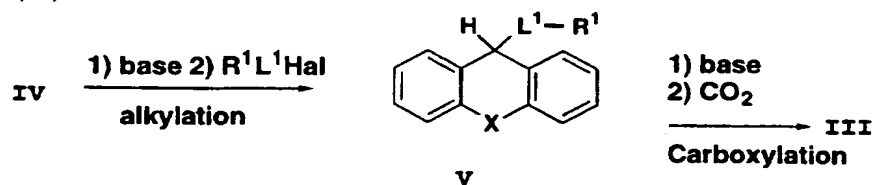
5 Scheme 1C

Preparation of Starting Acids II and Dianion III

(1)

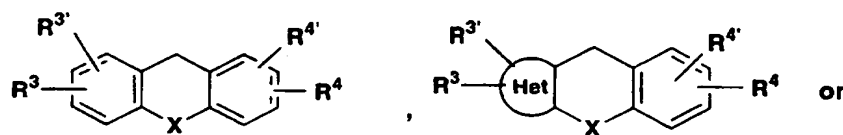


(2)

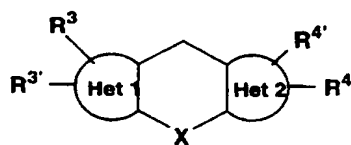


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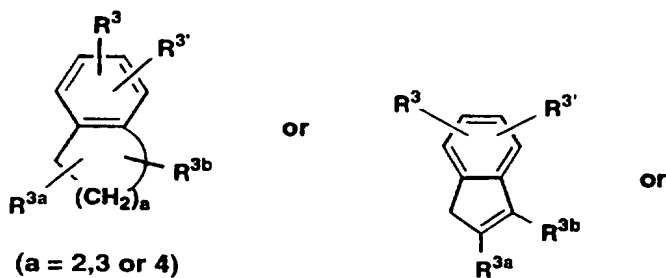
As indicated above, the starting Compound IV may also be



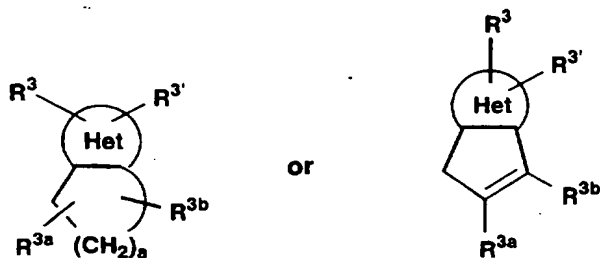
15



as well as



20



The above are collectively referred to "fluorenyl-type compounds".

- 5 As seen in Scheme 1A, in accordance with another aspect of the present invention, the solution of acid II in an inert organic solvent, such as tetrahydrofuran, dioxane or diethyl ether, at a reduced temperature of within the range of
- 10 from about -40°C to about room temperature, is treated with base such as potassium hydroxide, potassium tert-butoxide, lithium or potassium bis(trimethylsilylamide), or n-butyllithium in an inert organic solvent such as hexane,
- 15 tetrahydrofuran or diethyl ether, while maintaining temperature of the reaction mixture below from about -40°C to about room temperature. The reaction mixture is treated with R¹ halide such as an alkylhalide, for example, 3-phenylpropylbromide
- 20 to form the alkylated product III.

The above dianion formation reaction is carried out employing a molar ratio of R¹halide:acid II of within the range from about 10:1 to about 0.5:1, preferably from about 2:1 to

25 about 0.8:1.

Alternatively, the compound III may be prepared as shown in Scheme 1C(2) wherein fluorenyl-type compound IV is treated with base, such as described above, for example n-

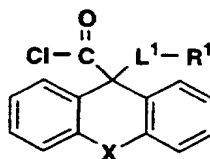
30 butyllithium, and then reacted with R¹halide, such as alkylhalide, as described above, to give compound V. Treatment of V with base, such as

described hereinbefore such as n-butyl-lithium, followed by treatment of the reaction mixture with CO₂ (carboxylation) gives III.

As seen in Scheme 1C(1), acid II may be
 5 formed by treating fluorenyl-type compound IV with base (as described above with respect to Scheme 1C(2), followed by treatment with CO₂ (carboxylation), to form II.

The amide Ia of the invention is formed by
 10 treating III with thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane (optionally in the presence of dimethylformamide (DMF)) to form the acid chloride IIIA

15



IIIA

Acid chloride IIIA, without separation from the reaction mixture, is treated with amine (R²L²)R⁵NH at a reduced temperature within the range from
 20 about -40°C to about room temperature, to form the amide Ia.

In carrying out the above reaction to form amide Ia, the amine will be employed in a molar ratio to acid chloride IIIA within the range from
 25 about 4:1, to about 1:1, optionally in the presence of a tertiary amine base or other acid scavenger.

Alternatively, as seen in Scheme 1B, amide I may be prepared by esterifying III (as shown in Scheme 6) by reacting III with a phenol such as
 30 phenol, 4-nitrophenol, or pentafluorophenol and DCC (dicyclo-hexylcarbodiimide) or EDCI (1-(3-dimethyl-amino-propyl)-3-ethylcarbodiimide), optionally in the presence of HOBT (1-hydroxybenzotriazole) through the intermediary of an aryl ester such as

phenyl, p-NO₂-phenyl or pentafluorophenyl, followed by treatment with a primary or secondary amine to give Ia.

- 5 In carrying out the above reaction, the amine will be employed in a molar ratio to ester within the range from about 10:1, to about 1:1.

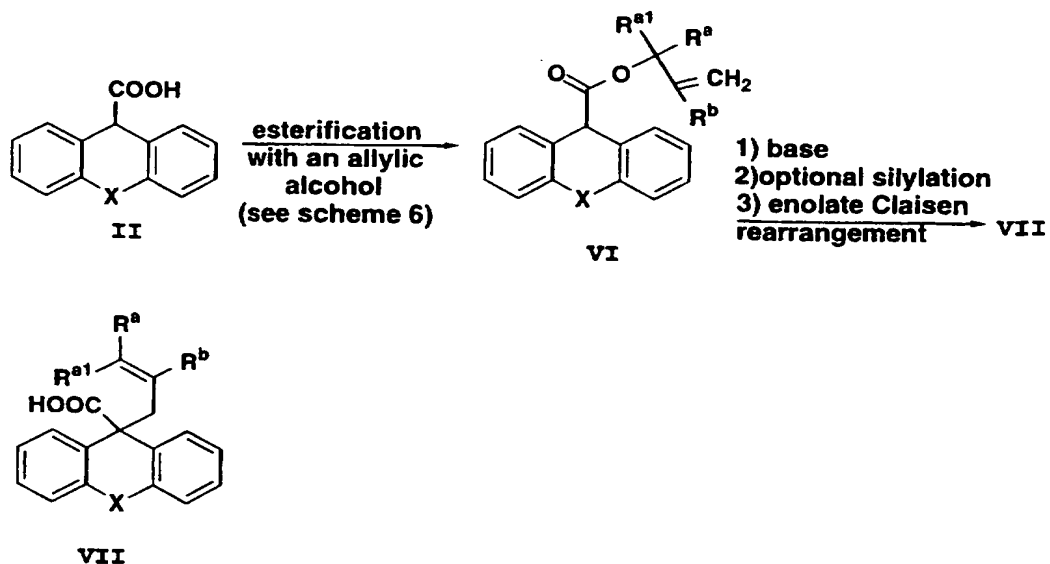
Alternative formation of amide Ia from acid III and R²R⁵NH can be carried out via standard literature procedures.

10

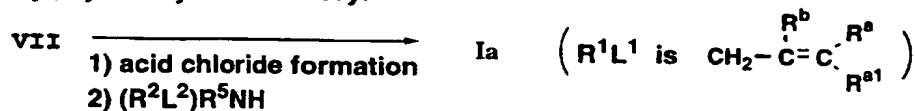
Reaction Scheme 2 (Amides)

Alternative Preparation of Compounds of Formula Ia

where A is $\begin{array}{c} \text{---N---} \\ | \\ \text{R}^5 \end{array}$



where R^a, R^{a1}, R^b independently are H, alkyl, aryl, cycloalkyl or heteroaryl



5

As seen in Reaction Scheme 2, amides of the invention of structure I can also be prepared by esterifying acid II with an allylic alcohol (as described in Scheme 5), to form ester VI which is treated with base, such as lithium diisopropyl amide or potassium bis(trimethylsilylamide) (optionally in the presence of a triorganosilylchloride, such as trimethylsilylchloride), to give the enolate-Claisen rearrangement acid product VII. Acid VII is then converted to amide Ia of the invention employing conditions as described with respect to Scheme 1.

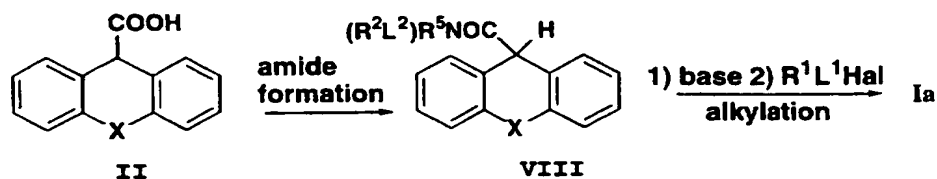
In carrying out the above reaction, the base treatment and enolate-Claisen rearrangement were performed at a temperature within the range of

from about -20 to about 100°C, preferably from about 25° to about 80°C, to form Ia where R^1L^1 is as defined above in Scheme 2.

5 Reaction Scheme 3 (Amides)

Alternative Preparation of Compounds of Formula Ic

where A = $\begin{array}{c} \text{---N---} \\ | \\ R^5 \end{array}$



10

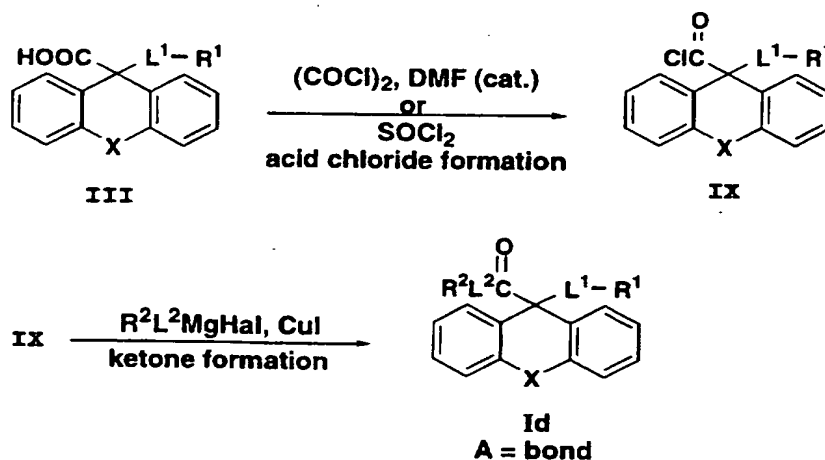
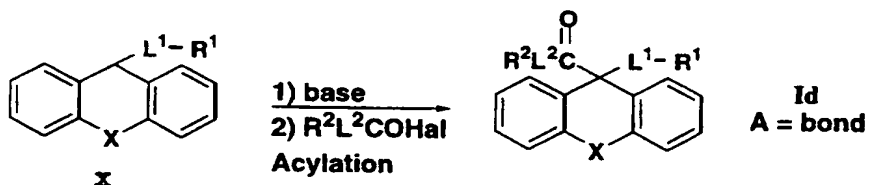
As seen in Reaction Scheme 3, compounds of structure I of the invention can be prepared optionally through amide formation (as described in Reaction Scheme 1 or via other known coupling procedures) from acid II to give compounds of formula VIII. Treatment of VIII with base, such as lithium diisopropylamide or n-BuLi, or potassium bis(trimethylsilyl)amide, followed by quenching the anion with an alkyl halide gives compounds of the formula I. In the specific case where R^5 is H, a dianion can be prepared requiring \geq two equivalents of base; the dianion can be trapped with an alkyl halide to give I.

15

20

Reaction Scheme 4

Preparation of Ketones I (A is a bond)

Scheme
4AScheme
4B

5

Compounds of the formula I of the invention wherein A = bond can be prepared as shown in Reaction Schemes 4A and 4B.

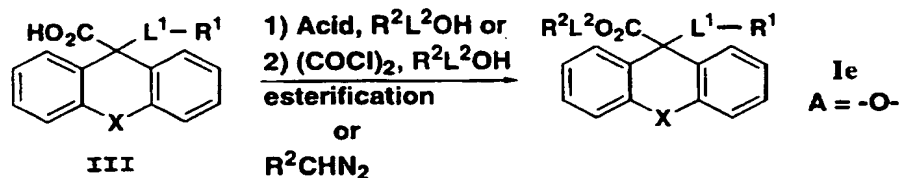
As seen in Scheme 4A, acid chloride formation under standard methods gives compound IX, which can be reacted with Grignard reagents and copper (I) iodide to give the compound of the invention I.

As seen in Scheme 4B, optionally, ketones can be formed by treatment of X with base, followed by acylation with an acid halide (R^2L^2COHal), preferably chloride or fluoride, to give compounds of the invention I.

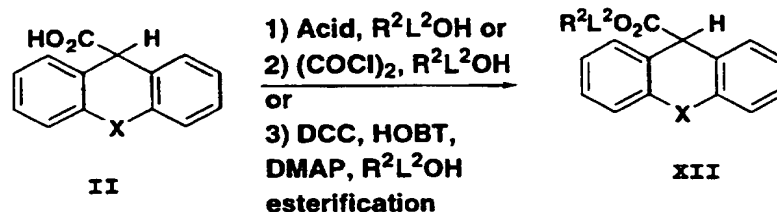
Reaction Scheme 5 (Class Esters)

Preparation of Esters I (A - -O-)

Scheme 5A:



Scheme 5B:



- 5 As seen in Reaction Scheme 5A, compounds of formula I of the invention wherein A = oxygen can be prepared by an acid catalyzed esterification of acid III employing an acid such as H_2SO_4 or p-toluene-sulfonic acid in the presence of an alcohol
- 10 such as allyl alcohol, ethanol or methanol. Alternatively, activation of the acid III to the acid chloride (with oxaly chloride or thionyl chloride) followed by treatment with an alcohol optionally in the presence of a tertiary amine base
- 15 or other acid scavenger, gives compounds of formula I.

- Various additional methods of activation include mixed anhydride formation ($(CF_3COO)_2$ or i-BuOCOC1) or formation of the acylimidazole
- 20 (carbonyldiimidazole) or with DCC and HOBT in the presence of DMAP (4-dimethylaminopyridine). These

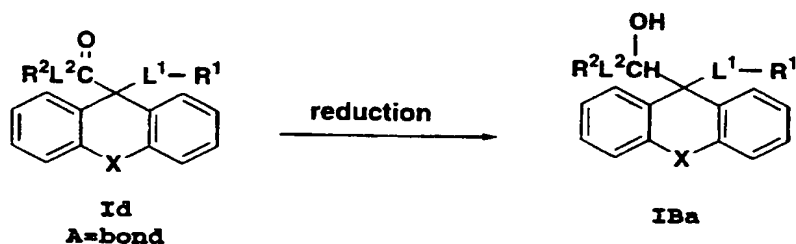
activated intermediates readily form esters upon treatment with alcohols.

Scheme 5B involves esterification of acids II to compound XII which is subjected to alkylation to give Ie.

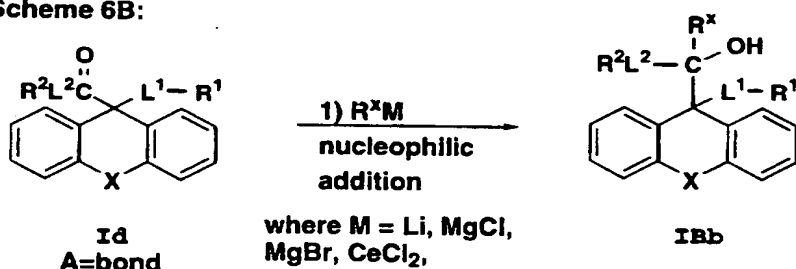
Reaction Scheme 6 (Class Alcohols IB)

Preparation of Alcohols (IB)

Scheme 6A:



Scheme 6B:



10

Compounds of formula Id, with A = bond, can be reduced by methods known in the art, such as sodium borohydride, to give alcohols of the invention IBa (Scheme 5A).

15

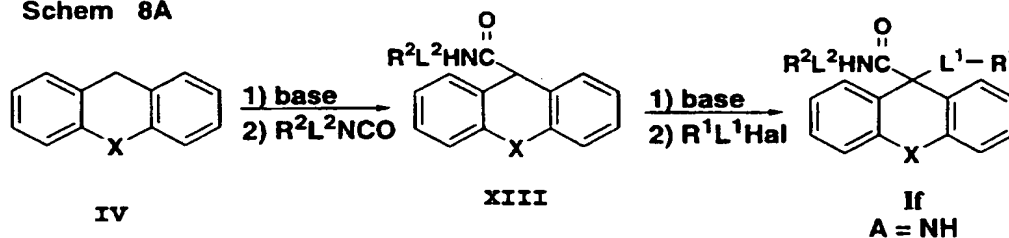
Ketones of formula Id can also be reacted with alkyl metals, such as alkyl lithium or Grignard reagents, to give the tertiary alcohols of the invention of structure IBb (Scheme 6B).

20

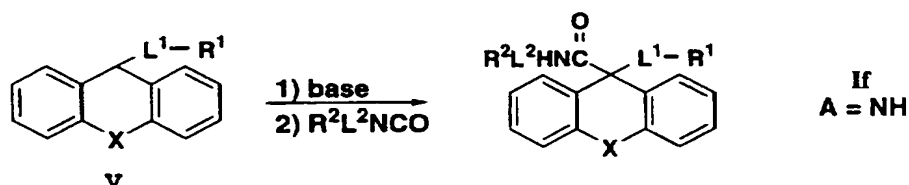
Reaction Scheme 7 (Amides from Isocyanates)

Preparation of Amides If (A is NH)

Schem 8A



Scheme 8B



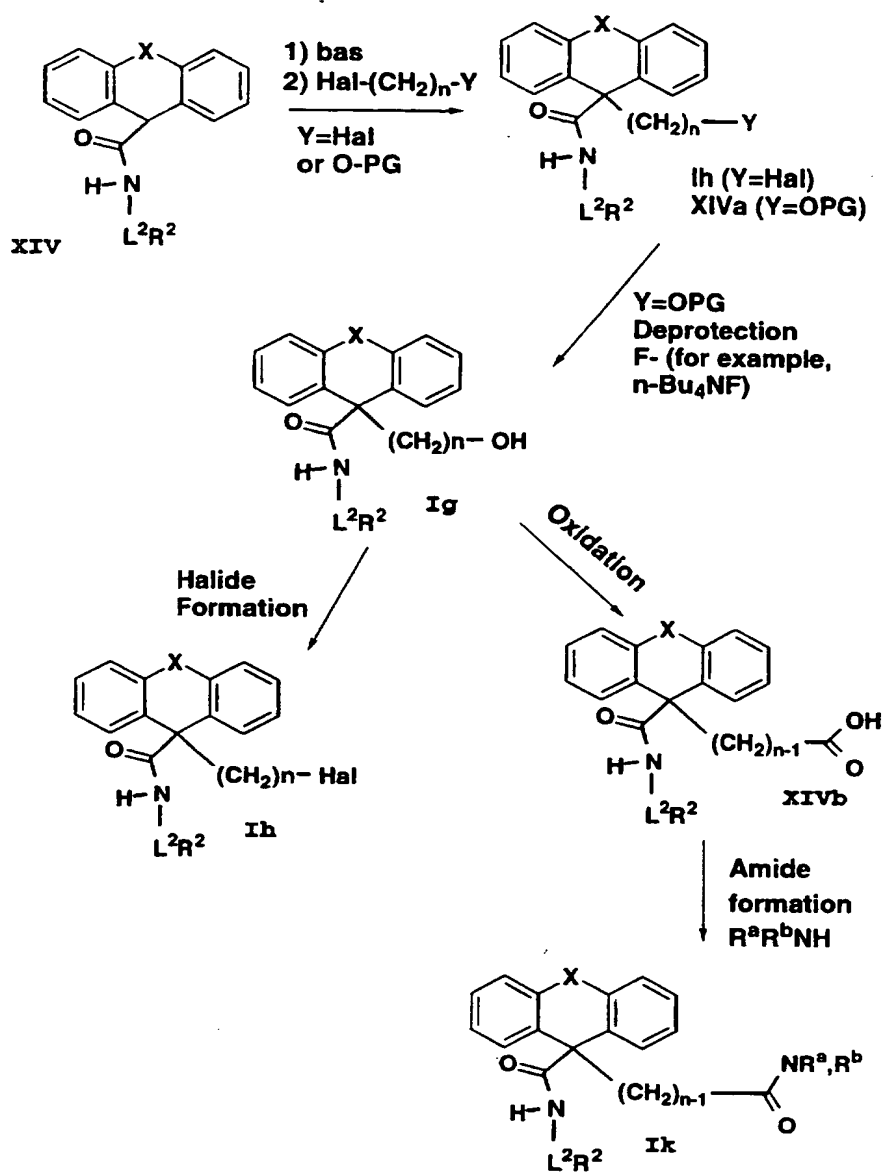
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Compounds of formula I where A is -NH- (amides) can be prepared by the methods shown in Reaction Scheme 7A from known compound IV.

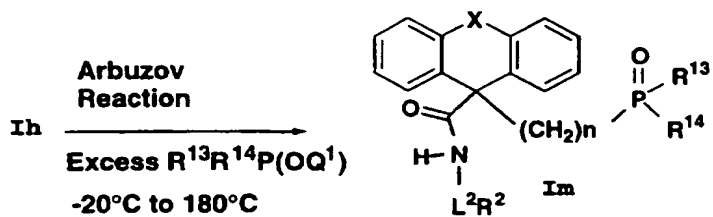
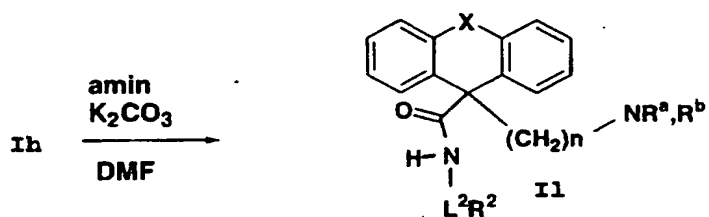
- 10 Treatment of compound IV with base, such as n-BuLi, followed by reacting the anion with an isocyanate gives compound XIII. Compound XIII can be further transformed to compounds of the formula If as shown above.

- 15 In a similar manner, as seen in Scheme 7B, compound V can be transformed to compounds of the formula If.

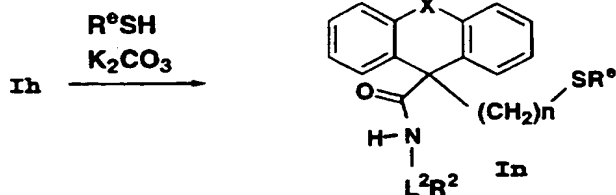
Reaction Scheme 8



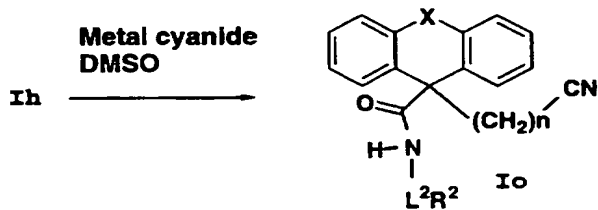
5 such where PG is an oxygen protecting group,
 as t-Bu(CH₃)₂Si or tBu(Ph)₂Si-



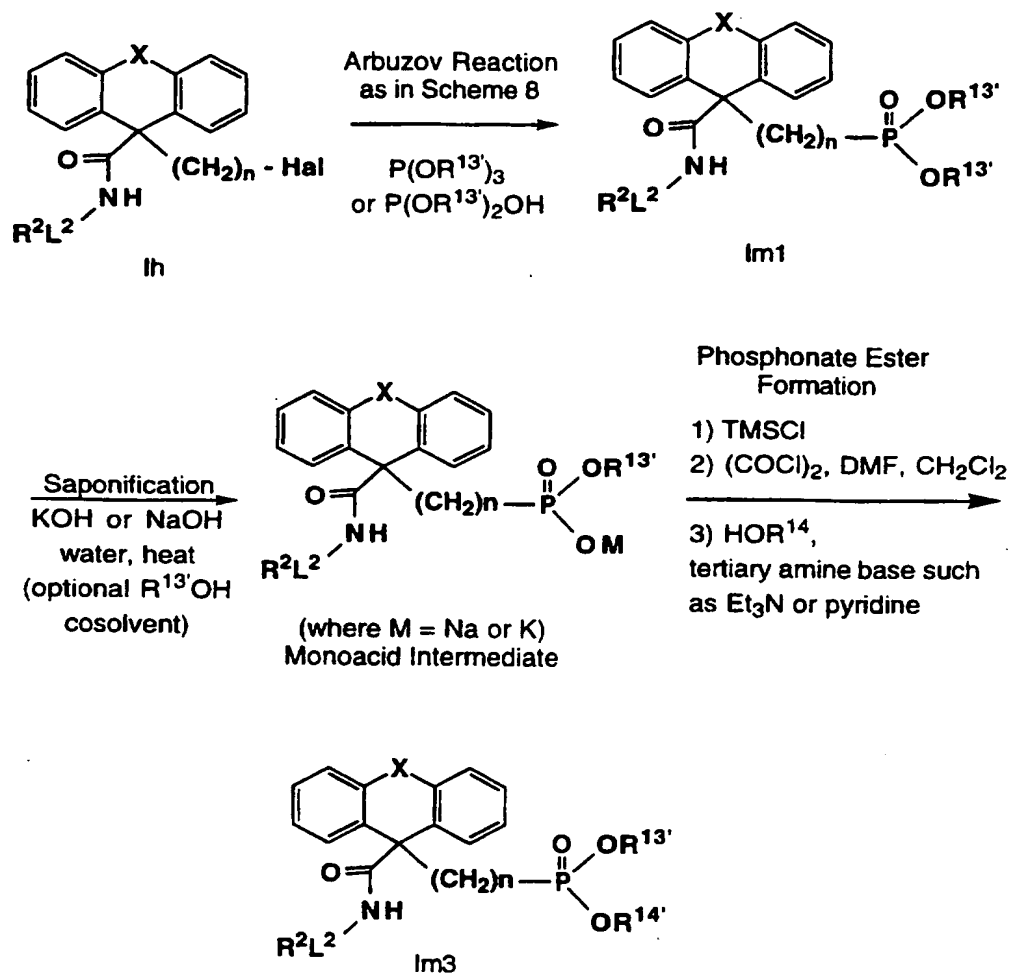
and Q^1 is alkyl, triorganosilyl (such as trimethylsilyl or t-butyl dimethylsilyl), H, the latter in the presence of base such as butyllithium, sodium hydride, or sodium bis-(trimethylsilylamide)



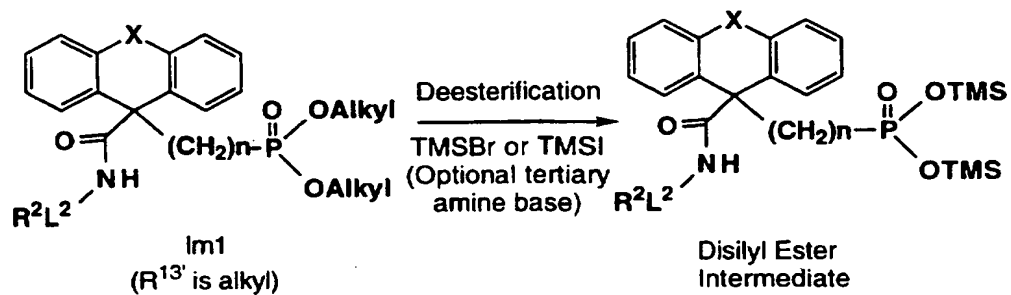
(R^e is alkyl, aryl, arylalkyl, heteroaryl, 2-benzthiazolyl, 2-imidazolyl)



Scheme 8A - Alternate Scheme for Compound Im
Scheme 8A

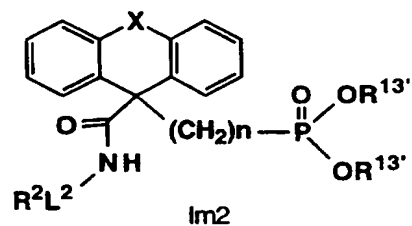


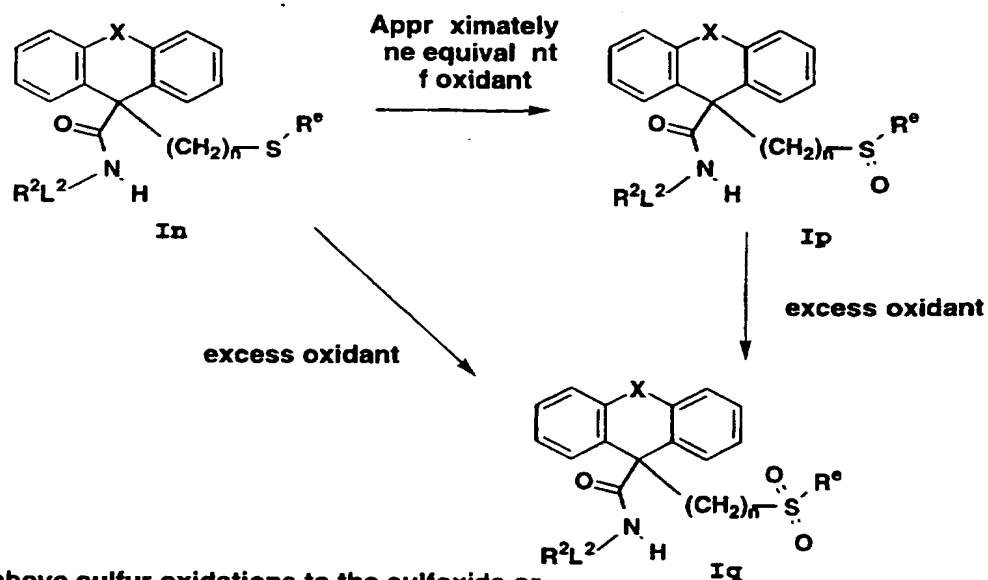
Scheme 8B



Phosphonate Ester Formation

- 1) $(COCl)_2$, DMF, CH_2Cl_2
- 2) $HOR^{13'}$,
tertiary amine base such as
 Et_3N or pyridine



Scheme 9 - Sulfur Oxidation

The above sulfur oxidations to the sulfoxide or sulfone are carried out by employing standard sulfur oxidation procedures in the art. Suitable oxidants include peracids (such as m-chloroperbenzoic acid) and sodium periodate.

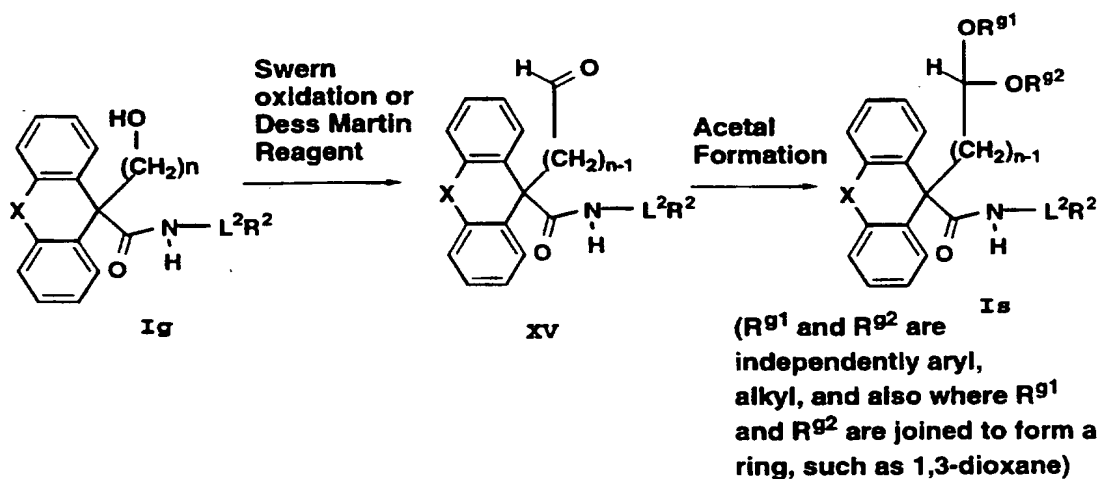
- 5 Compounds I of the invention may be modified by the various transformations set out in Reaction Scheme 8. Protected alcohol XIVa can be converted into a wide variety of functional groups through the intermediacy of a halide Ih. For
- 10 example, the alcohol Iq can be converted to the halide Ih of the invention by either activation through the sulfonate ester (tosyl chloride, or mesyl chloride) and iodide displacement (NaI or KI in acetone or 2-butanone), or by reaction with
- 15 triphenylphosphine, I_2 and imidazole. The iodide Ih can undergo an Arbuzov reaction to form phosphonates, phosphinates and phosphine oxides of the invention Im. The Arbuzov reaction can be accomplished with phosphites, phosphinites, and
- 20 phosphonites (for example, $\text{R}^{13}\text{R}^{14}\text{POalkyl}$ or $\text{R}^{13}\text{R}^{14}\text{POSi(alkyl)}_3$ or $\text{R}^{13}\text{R}^{14}\text{POH}$, the latter being in the presence of a base such as butyllithium, sodium hydride or sodium bis(trimethyl-silylamide)) at

temperatures within the range from about -20°C to about 180°C . Alternately, displacement reactions to form amines Ii , thioethers In or nitriles Io can be easily accomplished. To form amines Ii , iodide Ih , can be treated with amines in DMF with or without K_2CO_3 . Thioethers In can also be formed under similar conditions. The nitriles If are prepared from either KCN or NaCN in hot DMSO. The alcohol can also be oxidized to a carboxylic acid.

10 The acids can also be used as intermediates to form amides of the invention Ik by methods previously described. The sulfur atom of In can be oxidized under standard conditions to sulfoxide Ip or sulfone Iq .

15

Reaction Scheme 10 (Preparation of Acetals)

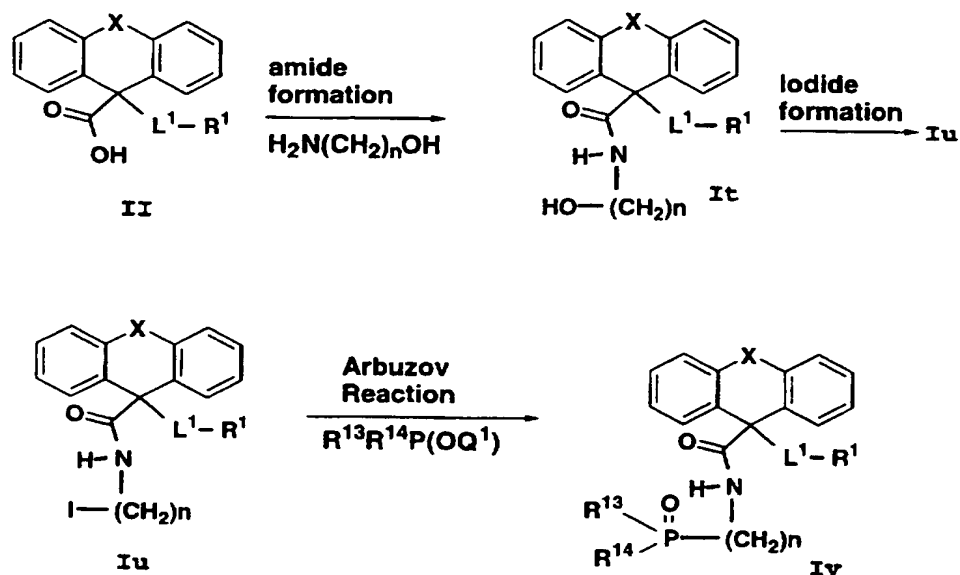


Acetals of the invention Is can be prepared from alcohol Ig by oxidation of the alcohol to the aldehyde xv . Preferred reagents to accomplish the transformation are either the Swern oxidation ($(\text{COCl})_2$, DMSO, triethylamine) or Dess-Martin Periodinane. The aldehyde xv can be converted to the acetal Is with excess alcohol such as 1,3-propanediol or ethylene glycol in the presence of a catalytic amount of acid such as H_2SO_4 or p-toluenesulfonic acid, optionally in the presence of

a dehydrating agent such as 4A sieves or trimethyl orthoformate.

Reaction Scheme 11

5 Preparation of Phosphonates in R²



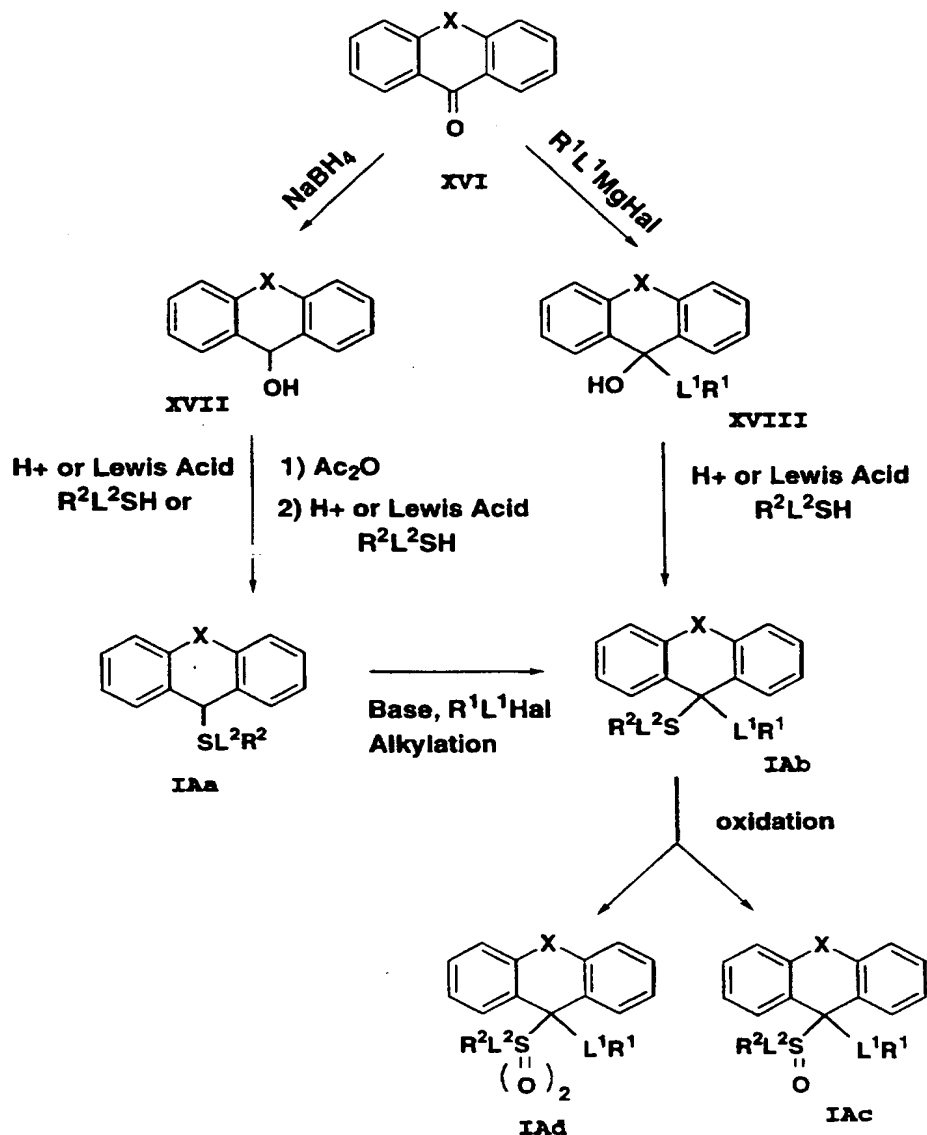
- An addition procedure to incorporate the phosphonate in the N-alkyl chain is shown in Scheme 11. Carboxylic acid II is converted to the amide of the invention It as follows. Activation of the acid II to the acid chloride (with oxalyl chloride or thionyl chloride) followed by treatment with an aminoalcohol such as 1,5-aminopentanol or 1,3-aminopropanol gives amide of the invention It. Various additional methods of activation include mixed anhydride formation ((CF₃COO)₂ or i-BuOCOC₂H₅) or formation of the acylimidazole (carbonyldiimidazole) or with DCC and HOBT in the presence of DMAP. These activated intermediates readily form amides upon treatment with aminoalcohols. The alcohol It can then be converted to the iodide Iu by either activation through the sulfonate ester (tosyl chloride or mesyl chloride) and iodide displacement (NaI or KI

in acetone or 2-butanone) or by reaction with triphenylphosphine, I_2 and imidazole. The iodide Iu can be reacted with a phosphorus (III) derivative $R^{13}R^{14}P(OQ^1)$, for example

- 5 triethylphosphite, tributylphosphite or (phenyl) $_2POC_2H_5$, in an Arbuzov reaction to give the phosphonate of the invention Iv.

Reaction Scheme 12

10 Preparation of Thioderivatives IA



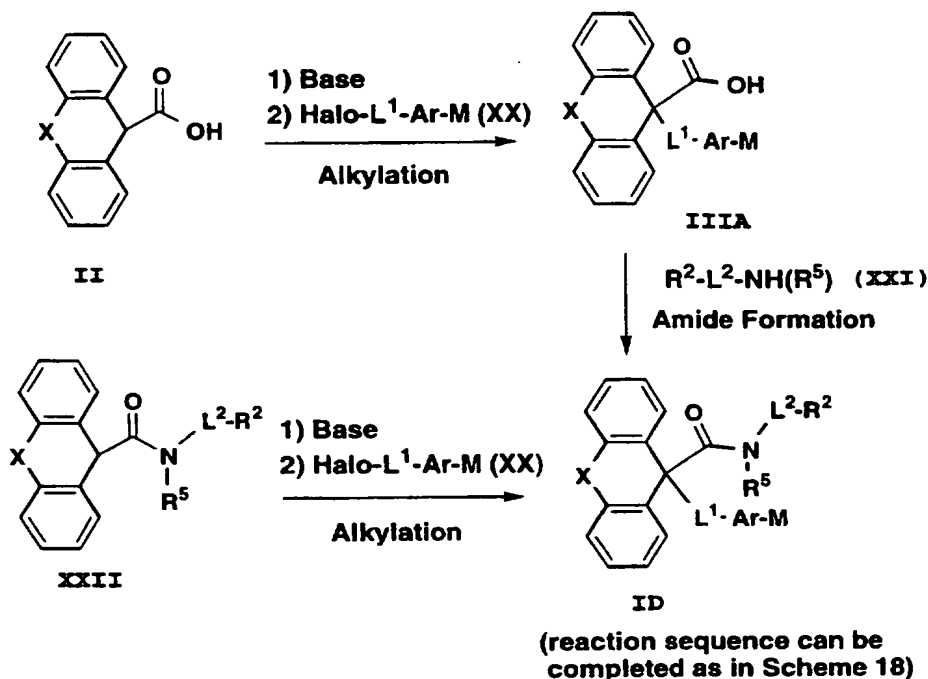
Reaction Scheme 12 outlines the general procedure for the preparation of the sulfides, sulfones and sulfoxides IA of the invention. Ketone XVI can be reduced with NaBH_4 to give alcohol XVII. The alcohol XVII can undergo solvolysis by treatment with acid (H_2SO_4 , or BF_3 -etherate, TiCl_4) in the presence of a thiol ($\text{R}^2\text{L}^2\text{SH}$) such as butanethiol to give thio compound of the invention IAa. An alternate method to give IAa proceeds via acetate formation (Ac_2O), followed by the solvolysis reaction. Thioether IAa can be alkylated ($n\text{-BuLi}$, $\text{R}^1\text{L}^1\text{Hal}$) by treatment with base and trapping with an alkyl halide to give sulfide of the invention IAb. The thioether in IAb can be oxidized to the sulfoxide IAc by mCPBA (m-chloroperbenzoic acid), or NaIO_4 . Sulfone IAd can be obtained from IAb by oxidation with, for example, mCPBA by employing 2 or more equivalents of oxidizing agent.

Alternately, ketone XVI can be reacted with a Grignard to give XVII which can undergo solvolysis reactions (H_2SO_4 , $\text{R}^2\text{L}^2\text{SH}$, or BF_3 -etherate, R^2SH) to give sulfide IAb. The sulfones and sulfoxides can be obtained as described above.

25

Reaction Scheme 13

Preparation of Compounds of Formula I where A is $\begin{array}{c} -N- \\ | \\ R^5 \end{array}$ where R^5 is preferably H and L^1 is a linking group as defined above.



1) Ar or Ar is aryl or heteroaryl

2) M is NO_2 , N-PG^1 , NHCOR^q , NHSO_2R^s , $\text{N(PG}^2\text{)COR}^q$, $\text{N(PG}^2\text{)SO}_2\text{R}^s$
Examples of protecting groups for nitrogen (PG^1) are Stabase ($-\text{Si}(\text{CH}_3)_2\text{-CH}_2\text{CH}_2\text{-(CH}_3)_2\text{Si-}$), BOC (t-Butylo-CO-), bis-BOC or phthalimido.

3) Examples of PG^2 are BOC, $(\text{CH}_3)_3\text{Si-}$ or $\text{t-Bu(CH}_3)_2\text{Si-}$

Compounds of the invention of formula I

where A is $\begin{array}{c} -N- \\ | \\ R^5 \end{array}$ and R^5 is preferably H, and L^1 is a
5 linking group as defined above can be prepared as shown in Reaction Scheme 13.

As seen in Scheme 13, acid II is treated
with base and alkylated by reaction with halide XX,
as described with respect to Scheme 1, to form
10 alkylated intermediate IIIA. IIIA is reacted with
amine XXI (using the amide formation procedure as
described in Scheme 1) to form amide of the
invention ID.

Where M in ID is NO₂, NHCOR^q or NHSO₂R^s, ID represents a final product.

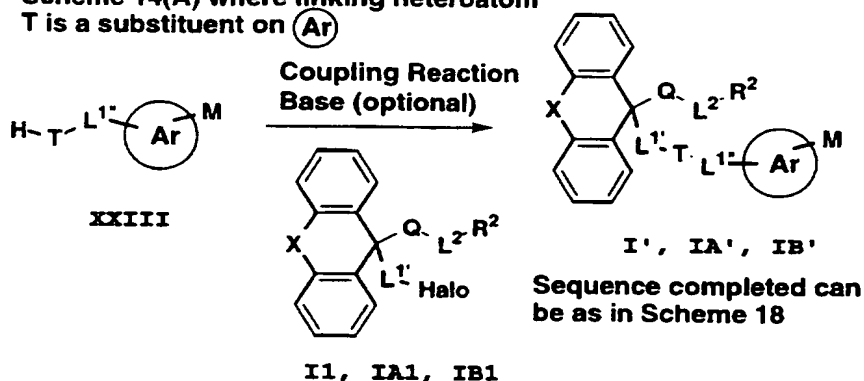
Where M includes a protecting group, the protecting group may be removed as shown in Scheme 18.

Where desired, acid II may undergo amide formation by reaction with amine XXI to form amide XXII via various known procedures, which is then alkylated to form ID.

Reaction Scheme 14

Preparation of Compounds I, IA or IB where R¹ is aryl or heteroaryl.

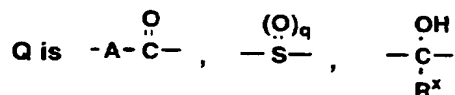
Scheme 14(A) where linking heteroatom T is a substituent on (Ar)



M and (Ar) are defined as in Scheme 13.

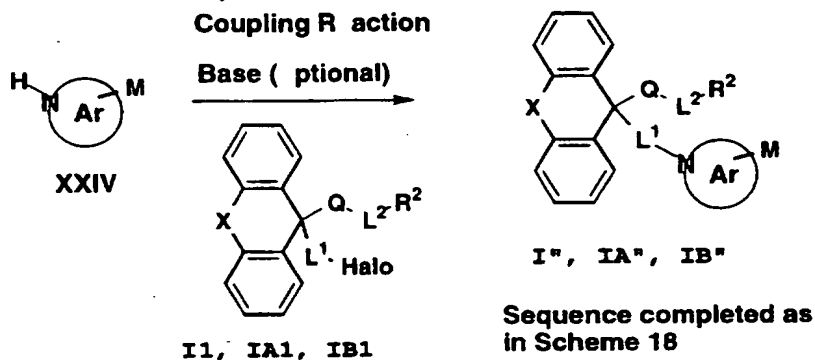
T is either

- (1) a heteroatom (O, NH, N(alkyl) or S), as a substituent on (Ar) linked to (Ar) via the linker L^{1*}, where L^{1*} can either be a bond, or is defined as is L¹, or (as depicted below)
 - (2) a nitrogen atom, as a ring member of Ar, in which case L^{1*} does not exist
- L^{1*} is a linker such as defined for L¹, or a bond.



Note that the group $-L^{1*}-T-L^{1*}-$ defines L¹.

Scheme 14(B) where the linking nitrogen is a ring member of (Ar)



Compounds of the invention of formula I, IA or IB where R¹ is aryl or heteroaryl may be prepared as shown in Reaction Schemes 14(A) and 14(B).

In Scheme 14(A) compounds of formula I', IA' or IB' (where R¹ is aryl or heteroaryl) may be prepared by coupling compound XXIII with compound II, IA1 or IB1, respectively, optionally in the presence of a base as described with respect to Scheme 1.

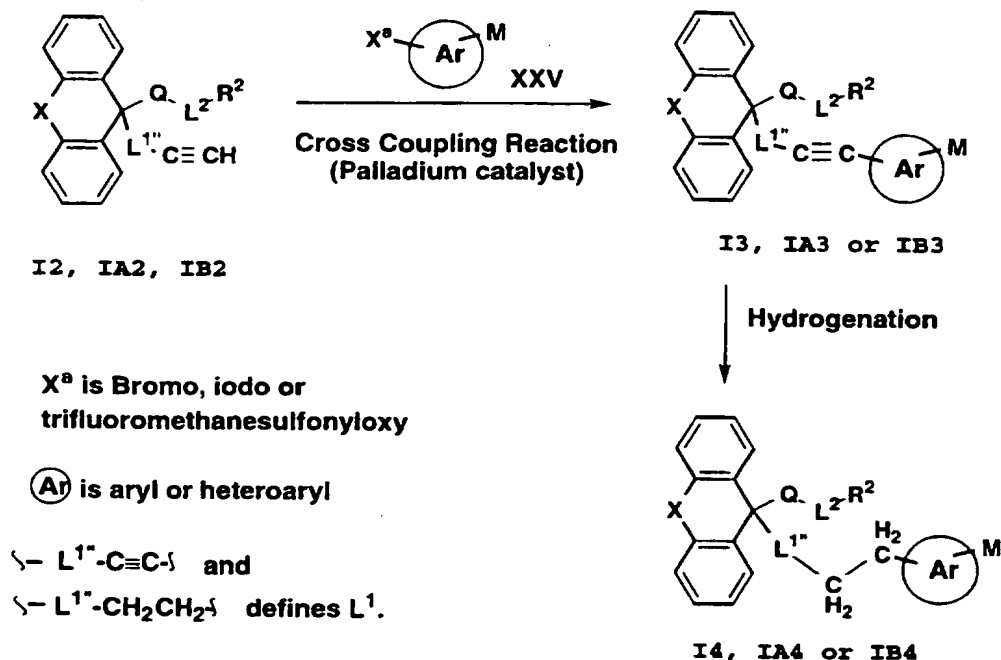
Compounds I', IA', IB', I'', IIA'' and IB'' may be subjected to deprotection and/or further converted, where necessary as shown in Scheme 18.

In Scheme 14(B) compounds of formula I'', IA'' or IB'' (where R¹ is heteroaryl and (Ar) is linked to L¹ via a ring nitrogen)) may be prepared by coupling XXIV with II, IA1 or IB1, optionally in the presence of a base.

Reaction Scheme 15

Preparation of Compounds I, IA or IB where R^1 is \textcircled{Ar}

Sequence completed as in Scheme 18



(Sequence can be completed as in Scheme 18)

Compounds of the invention of formula I, IA or IB where R^1 is \textcircled{Ar} may be prepared as shown in

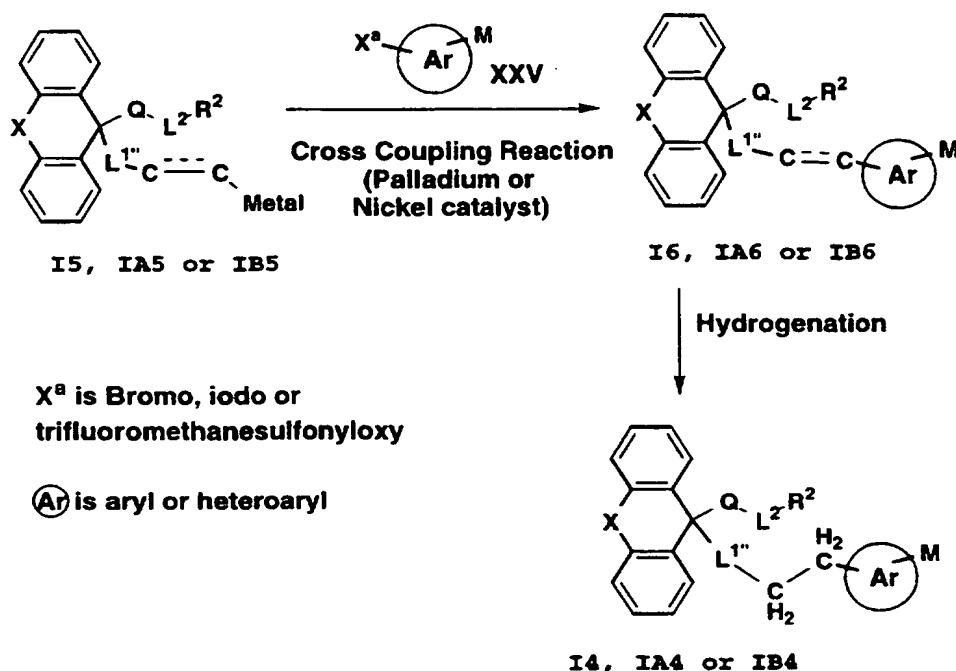
5 Reaction Scheme 15.

In Scheme 15, acetylenic starting compound I2, IA2 or IB2 is made to undergo a Castro-Stevens cross coupling with XXV in the presence of a catalyst, such as palladium, $Pd(Ph_3P)_4$ or $Pd(Ph_3P)_2Cl_2$ in the presence of an amine (e.g. $BuNH_2$, Et_3N) and a Copper (I) salt (e.g. CuI) to form compound of the invention I3, IA3 or IB3, respectively, and subjecting I3, IA3 or IB3 to hydrogenation to form compound of the invention I4, IA4 or IB4.

Compound I3, IA3, IB3, I4, IA4 or IB4 may be subjected to deprotection and further conversion if necessary, as described in Reaction Scheme 18.

Reaction Scheme 16

Alternative Preparation of Compounds I, IA or IB where R¹ is (Ar)



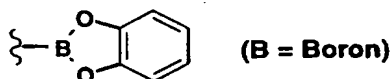
X^a is Bromo, iodo or trifluoromethanesulfonyloxy

(Ar) is aryl or heteroaryl

Sequence can be completed as in Scheme 18

C=C represents a single or double C-C bond, and if a double bond can have either cis or trans stereochemistry.

Metal can be ZnHalo, MgHalo, SnBu₃, B(alkyl)₂, B(OH)₂

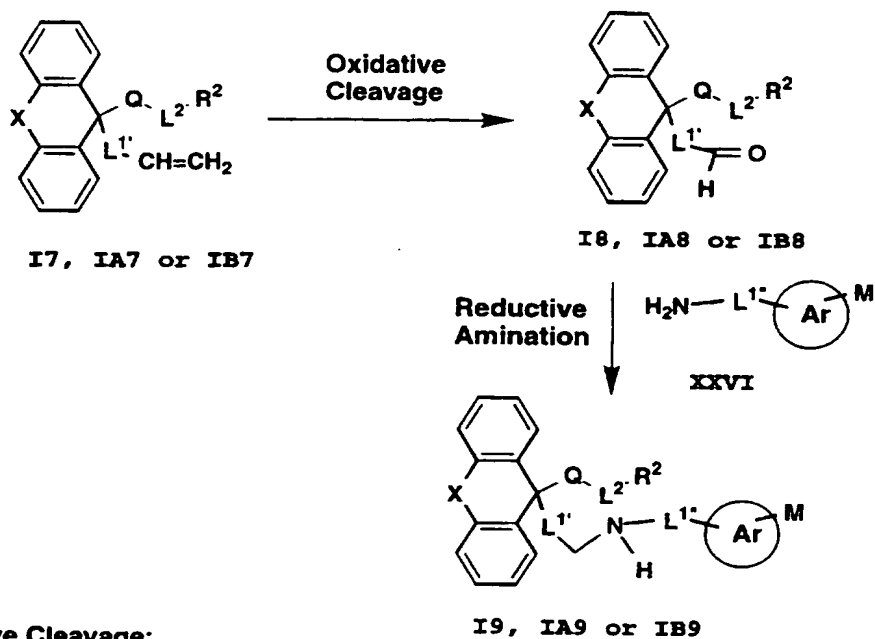


{-L¹-CH₂-CH₂-} and {-L¹-C=C-C-} define the linker L¹

- In an alternative procedure as shown in
- 5 Reaction Scheme 16 compound I4, IA4 or IB4 may be prepared starting with compound I5, IA5 or IB5, respectively, which is made to undergo a cross coupling reaction with XXV in the presence of a palladium or nickel catalyst, to form I6, IA6 or
 - 10 IB6, respectively, which is hydrogenated to form I4, IA4 or IB4, respectively.

Reaction Scheme 17

Preparation of Compounds I, IA or IB where L¹ is an N-containing moiety



Oxidative Cleavage:
Ozone in CH₂Cl₂ or CH₃OH,
at low temperature (-78°C to 25°C)
followed by reductive workup
Ph₃P, (CH₃)₂S or Zn, acetic acid;
alternatively, use NaIO₄/OsO₄ in
t-BuOH or THF, or mixtures
with optional water added
(Lemieux-Johnson reaction).

Sequence can be completed
as in Scheme 18

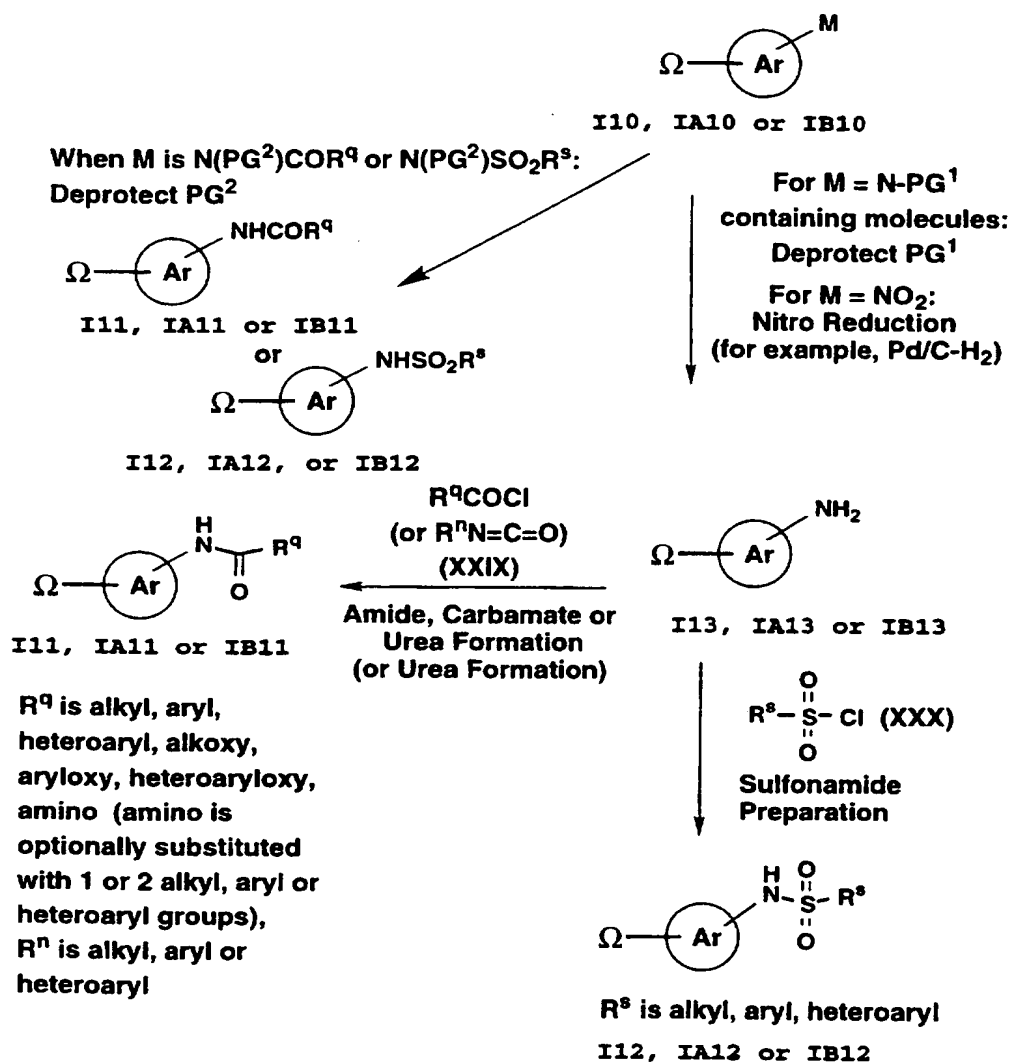
Note that -L¹CH₂NHL¹ defines L¹

Reductive amination: NaBH₄, NaBH₃CN
or NaB(OAc)₃H, in CH₂Cl₂, MeOH, i-PrOH,
t-BuOH, THF, DMF or mixtures thereof,
optionally in the presence of an acid catalyst
such as HCl or Ti(OCH(CH₃)₂)₄.

- Compounds of the invention of formula I, IA or IB where L¹ is an N-containing moiety may be prepared as shown in Reaction Scheme 17 wherein starting compound I7, IA7 or IB7 is made to undergo
- 5 oxidative cleavage, as described above, to form aldehyde I8, IA8 or IB8, respectively, which is subjected to reductive amination by reaction with amine XXVI, as described above, to form compound of the invention I9, IA9 or IB9, respectively.
- 10 Compound I9, Ia9 or IB9 may undergo deprotection, if necessary, as shown in Scheme 18.

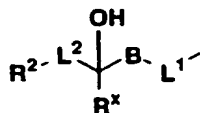
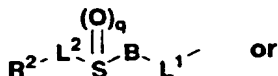
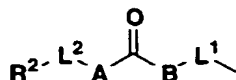
Reaction Scheme 18

Preparation of final products from M containing intermediates in Schemes 13 to 17



In a preferred method, superior yields of final products (I11, IA11, IB11, I12, IA12, IB12) are obtained when the intermediate I13, IA13, IB13 is reacted with R^qCOCl , $\text{R}^n\text{N}=\text{C}=\text{O}$ or $\text{R}^s\text{SO}_2\text{Cl}$ immediately after formation of I13, IA13 or IB13, preferably in situ.

1) Ω repr sents



2) \textcircled{Ar} is aryl or heteroaryl

3) M is NO_2 , N-PG, NHCOR^q , NHSO_2R^s , $\text{N}(\text{PG}^2)\text{COR}^q$, $\text{N}(\text{PG}^2)\text{SO}_2\text{R}^s$

Examples of protecting groups for nitrogen (PG^1) are Stabase
 $(-\text{Si}(\text{CH}_3)_2-\text{CH}_2\text{CH}_2-(\text{CH}_3)_2\text{Si}-)$, BOC (t-Butylo-CO-) and bis-BOC.

4) Examples of PG^2 are BOC, $(\text{CH}_3)_3\text{Si}-$ or t-Bu $(\text{CH}_3)_2\text{Si}-$

5) Deprotection according to the prior art.

The compounds of the invention may be employed in preventing, stabilizing or causing regression of atherosclerosis in a mammalian species by administering a therapeutically effective amount of a compound to decrease the activity of MTP.

The compounds of the invention can be tested for MTP inhibitory activity employing the procedures set out in U.S. application Serial No. 117,362 filed September 3, 1993, employing MTP isolated from one of the following sources:

- (1) bovine liver microsomes,
- (2) HepG₂ cells (human hepatoma cells) or
- (3) recombinant human MTP expressed in baculovirus.

The compounds of the invention may also be employed in lowering serum lipid levels, such as cholesterol or triglyceride (TG) levels, in a mammalian species, by administering a therapeutically effective amount of a compound to decrease the activity of MTP.

The compounds of the invention may be employed in the treatment of various other conditions or diseases using agents which decrease activity of MTP. For example, compounds of the invention decrease the amount or activity of MTP and therefore decrease serum cholesterol and TG levels, and TG, fatty acid and cholesterol absorption and thus are useful in treating hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, pancreatitis, hyperglycemia and obesity.

The compounds of the present invention are agents that decrease the activity of MTP and can be administered to various mammalian species, such as monkeys, dogs, cats, rats, humans, etc., in need of such treatment. These agents can be administered systemically, such as orally or parenterally.

The agents that decrease the activity or amount of MTP can be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable formulation. The above dosage forms will also include the necessary physiologically acceptable carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to the age, weight, and condition of the patient, as well as the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms described above may be administered in amounts of from about 5 to about 500 mg per day in single or divided doses of one to four times daily.

The following Examples represent preferred embodiments of the invention. All temperatures are in °C unless indicated otherwise.

Where structures are set in the following Examples which include hetero atoms with unfilled valency, it will be understood that hydrogen is attached to such hetero atoms to fulfill valency requirements.

10

Example 1

N-(Phenylmethyl)-9-(3-phenylpropyl)-9H-fluorene-9-carboxamide

15

A. N-(Phenylmethyl)-9H-fluorene-9-carboxamide

20

A solution of 9-fluorene carboxylic acid (2.10 g, 10.0 mmol) in 50 mL of CH₂Cl₂ was treated with oxalyl chloride in dichloromethane (6.0 mL, 12.0 mmol) and two drops of DMF. After 0.75 h, the mixture was concentrated under reduced pressure to give a white solid. The solid was diluted with 50 mL of CH₂Cl₂, cooled to 0°C, treated with benzylamine (1.17 g, 11.0 mmol) and pyridine (0.87 g, 11 mmol). The transparent yellow solution was stirred for 3 h at room temperature and diluted with ethyl acetate and water. The organic fraction was dried over Na₂SO₄ and concentrated to a white solid. The solid purified by trituration with hexanes and recrystallization from hot methanol to give 2.60 g (86%) of title compound as white flakes. mp 195-200°C.

30

TLC Silica gel (3:7 ethyl acetate/hexane) R_f = 0.30.
Mass Spec. (CI-NH₃, + ions) m/z 300 (M+H), 317
(M+NH₄).

35

Anal. Calc'd for $C_{21}H_{17}NO$:

C, 84.25; H, 5.72; N, 4.68

Found: C, 83.96; H, 5.68; N, 4.54.

5 B. N-(Phenylmethyl)-9-(3-phenylpropyl)-9H-fluorene-9-carboxamide

To a suspension of Part A compound (0.35 g, 1.17 mmol) in THF (10 mL) at 0°C was added n-butyllithium in hexanes (1.0 mL, 2.4 mmol) dropwise at such a rate to maintain the internal temperature near 0°C. The resulting bright orange solution was stirred at 0°C for 0.5 h and treated with 1-bromo-3-phenylpropane (0.26 g, 1.30 mmol). The mixture was slowly warmed to room temperature and stirred for 3 h and diluted with NH_4Cl (20 mL) and ethyl acetate (50 mL). The layers were separated, the organic fraction dried (Na_2SO_4) and concentrated. The remainder was purified by column chromatography on silica gel (30 g) with 2:8 ethyl acetate/hexane to give 0.33 g (67%) of title compound as a white solid. The solid was recrystallized from hot hexane to give 0.25 g (51%) of title compound as white flakes. mp 94°C.

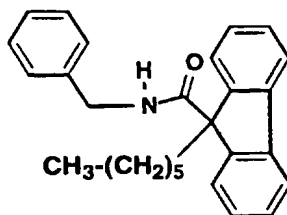
25 TLC Silica gel (3:7 ethyl acetate/hexane) R_f = 0.70.
Mass Spec. (CI- NH_3 , + ions) m/z 418 (M+H), 435 (M+ NH_4).

Anal. Calc'd for $C_{30}H_{27}NO$:

30 C, 86.30; H, 6.52; N, 3.35

Found: C, 85.99; H, 6.47; N, 3.21.

Examples 2-4 were prepared from Example 1 Part A by the method described in Example 1, Part B.

Example 2

5 MS ($\text{Cl}-\text{NH}_3$, + ions) m/e 384 (M+H).

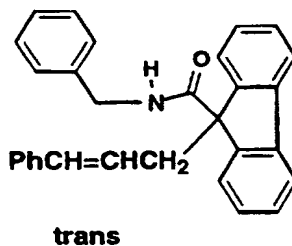
mp: 79-82°

Anal. Cald'd for $\text{C}_{27}\text{H}_{29}\text{NO}$:

C, 84.56; H, 7.62; N, 3.65

Found: C, 84.22; H, 7.72; N, 3.65.

10

Example 3

15 MS ($\text{Cl}-\text{NH}_3$, + ions) m/e 416 (M+H).

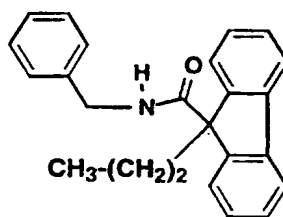
mp: 134°

Anal. Cald'd for $\text{C}_{30}\text{H}_{25}\text{NO}$:

C, 86.72; H, 6.06; N, 3.37

Found: C, 86.61; H, 6.23; N, 3.31.

20

Example 4

5 MS (Cl-NH₃, + ions) m/e 342 (M+H), 359 (M+NH₄).

mp: 96°

Anal. Calcd'd for C₂₄H₂₃NO:

C, 84.42; H, 6.79; N, 4.10

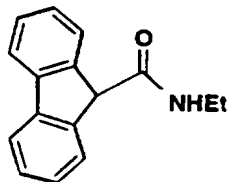
Found: C, 84.29; H, 6.72; N, 3.96.

10

Example 5

(E)-N-Ethyl-9-(3-phenyl-2-propenyl)-9H-fluorene-9-carboxamide

A.



15

A solution of 9-fluorene carboxylic acid (2.10 g, 10.0 mmol) in 50 mL of CH₂Cl₂ was treated with oxalyl chloride in dichloromethane (6.0 mL, 12.0 mmol) and two drops of DMF. After 0.75 h, the mixture was concentrated under reduced pressure to give a white solid. The solid was diluted with 50 mL of CH₂Cl₂, cooled to 0°C, treated with ethylamine (1.0 g, 22 mmol). The transparent yellow solution was stirred for 3 h at room temperature and diluted with ethyl acetate and water. The organic fraction was dried over Na₂SO₄ and concentrated to a white solid. The solid purified by trituration with hexanes and recrystallization from hot methanol to give 2.60 g

(86%) of title compound as white flakes. mp 233-234°C.

5 B. (E)-N-Ethyl-9-(3-phenyl-2-propenyl)-9H-
 fluorene-9-carboxamide

To a suspension of Part A compound (1.00 g, 4.21 mmol) in THF (25 mL) at 0°C was added n-butyllithium in hexanes (3.53 mL, 8.84 mmol) dropwise at such a rate to maintain the internal
10 temperature near 0°C. The resulting bright yellow solution was stirred at 0°C for 0.5 h and treated with cinnamyl chloride (0.79 g, 4.63 mmol). The mixture was slowly warmed to room temperature and stirred for 2 h when it was diluted with water (40
15 mL) and ethyl acetate (40 mL). The layers were separated, the organic fraction dried (Na₂SO₄) and concentrated. The remainder was triturated with hexanes and the resulting solid recrystallized from hot methanol to give 1.20 g (79%) of title compound
20 as white needles. mp 144°C.

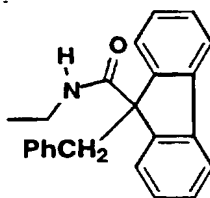
TLC Silica gel (3:7 ethyl acetate/hexane) R_f=0.6.

Anal. Calc'd for C₂₅H₂₃NO:

25 C, 84.95; H, 6.56; N, 3.96

Found: C, 84.53; H, 6.74; N, 3.95.

Example 6-10 can be prepared from Example 5
Part A compound by the method described in Example
30 5 Part B.

Example 6

5 MS (Cl-NH₃, + ions) m/e 328 (M+H).

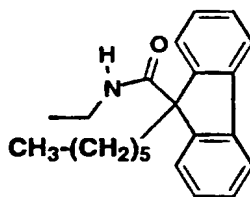
mp: 126-128°

Anal. Cald'd for C₂₃H₂₁NO:

C, 84.37; H, 6.46; N, 4.29

Found: C, 84.22; H, 6.42; N, 4.58.

10

Example 7

15 MS (Cl-NH₃, + ions) m/e 322 (M+H).

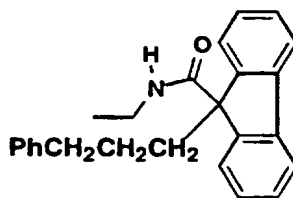
mp: 70°

Anal. Cald'd for C₂₂H₂₇NO:

C, 82.20; H, 8.47; N, 4.36

Found: C, 82.07; H, 8.55; N, 4.74.

20

Example 8

25 MS (Cl, + ions) m/z 356 (M+H).

mp: 72-73°

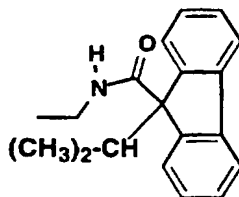
Anal. Cald'd for $C_{25}H_{25}NO + 0.3 H_2O$:

C, 83.08; H, 7.16; N, 3.88

Found: C, 82.84; H, 7.89; N, 3.78.

5

Example 9



MS (Cl-NH₃, + ions) m/e 280 (M+H).

10 mp: 66-67°

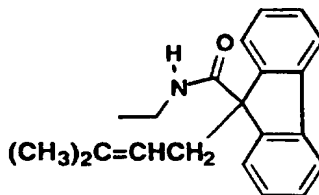
Anal. Cald'd for $C_{19}H_{21}NO$:

C, 81.68; H, 7.58; N, 5.01

Found: C, 81.60; H, 7.87; N, 5.08.

15

Example 10



MS (Cl-NH₃, + ions) m/e 306 (M+H).

20 mp: 78°

Anal. Cald'd for $C_{21}H_{23}NO$:

C, 82.59; H, 7.59; N, 4.59

Found: C, 82.37; H, 7.74; N, 4.57.

25

Example 11

9-[4-(Dibutoxyphosphinyl)butyl]-N-propyl-9H-
fluorene-carboxamide

A. N-Propyl-9-fluorene-carboxamide

A solution of 9-fluorene carboxylic acid (20.0 g, 95 mmol) in 200 mL of CH₂Cl₂ was treated with oxalyl chloride (12.5 g, 105 mmol) and 0.2 mL of DMF. After 0.75 h, the mixture was concentrated under reduced pressure to give a white solid. The solid was diluted with 100 mL of THF cooled to -40°C, treated with propylamine (11.8 g, 200 mmol). The suspension was stirred for 3 h at room temperature and diluted with ethyl acetate and water. The organic fraction was dried over Na₂SO₄ and concentrated to a white solid. The solid purified by trituration with hot hexanes and recrystallization from hot methanol to give 17.5 g (87%) of title compound as white flakes. mp 197-199°C.

TLC Silica gel (3:7 ethyl acetate/hexane) R_f= 0.30.

MS (CI-NH₃, + ions) m/e 252 (M+H).

B. Dibutyl (4-bromobutyl)phosphonate

A mixture of 1,4-dibromobutane (129 g, 600 mmol) and tributyl phosphite (15.0 g, 60 mmol) was heated to 118°C (bath temperature) for 6 h. The volatiles were removed by short path distillation (0.4 mm Hg, 40°C) to leave 20 g (100%) of part b compound as an amber colored oil. The oil can be purified by flash column chromatography on silica gel with 1:9 acetone/dichloromethane.

TLC: (1:9 acetone/dichloromethane) R_f=0.55.

¹³C NMR (d₆-acetone) δ 64.4 (d, J=6 Hz), 33.1, 33.0 (d, J=22 Hz), 32.4 (d, J=6 Hz), 24.0 (J=140 Hz), 21.1 (J=5 Hz), 18.5, 13.0 ppm.

C. Dibutyl (4-Iodobutyl)phosphonate

A mixture of Part B compound (4.8 g, 14.58 mmol), potassium iodide (20.0 g, 120 mmol) and acetone (200 mL) was heated to reflux for 2.5 h and
5 cooled to room temperature. The solids were filtered and the filtrate concentrated. The remainder was diluted with ether and filtered. The ether fraction was concentrated to give 5.32 g (97%) of title compound as a pale yellow oil.

10

TLC: (1:9 acetone/dichloromethane) $R_f=0.55$.

^{13}C NMR (CDCl_3) δ 65.2 (d, $J=7$ Hz), 33.7 (d, $J=17$ Hz), 32.4 (d, $J=6$ Hz), 24.2 ($J=140$ Hz), 18.6, 13.5,
15 5.5 ppm.

D. 9-[4-(Dibutoxyphosphinyl)butyl]-N-propyl-9H-fluorene-9-carboxamide

A solution of Part A compound (3.00 g, 11.95 mmol) in 30 mL of THF at -40° was treated
20 with n-BuLi (5.20 mL, 13 mmol) in hexanes at such a rate to maintain the internal temperature below -35° . The orange yellow solution was stirred for 0.5 h and treated with Part C compound (4.30 g, 11.50 mmol).
25 The mixture was warmed to room temperature over 0.5 h and after 2 h at room temperature was quenched with 100 mL of NH_4Cl solution and 100 mL of ethyl acetate. The organic fraction was dried (MgSO_4) and concentrated. The
30 remainder was purified by column chromatography on silica gel (400 g) with 1:9 acetone/dichloromethane to give 4.30 g (75%) of title compound as a colorless oil.

35 TLC Silica gel (7:3 ethyl acetate/hexane) $R_f=0.5$.
Mass Spec. (ES, + ions) m/e 500 ($\text{M}+\text{H}$).

Anal. Calc'd for $C_{29}H_{42}NO_4P + 0.6 H_2O$:

C, 68.29; H, 8.53; N, 2.75; P, 6.07

Found: C, 68.34; H, 8.45; N, 2.70; P, 6.03.

5

Example 12

(E)-9-(3-Phenyl-2-propenyl)-N-propyl-9H-fluorene-9-carboxamide

- 10 To a suspension of 500 mg (1.99 mmol) of Example 11 Part A compound in 10 mL of THF, at 0°C under argon, was added dropwise 2.5 mL (3.98 mmol) of n-BuLi (1.6 M in hexanes). The resulting orange solution was stirred at 0°C for 0.5 h at which time 305 µL (2.19 mmol) of cinnamyl chloride was added.
- 15 The reaction was warmed to RT and allowed to stir for 1 h at which time it was diluted with 1:1 ethyl acetate/water (30 mL). The organics were dried (NaSO₄) and evaporated to dryness. Purification by crystallization from hot methanol provided 350 mg
- 20 (48%) of title compound as a white solid.

mp 95-97°C.

TLC Silica gel (1:1 hexanes/ethyl acetate) R_f = 0.59.

- 25 MS (CI-NH₃, + ions) m/e 368 (M+H).

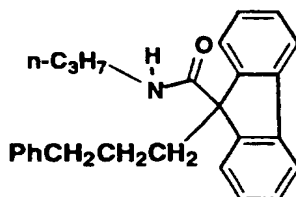
Anal. calcd. for $C_{26}H_{25}NO + 0.62 \text{ mol } H_2O$:

C, 82.47; H, 6.98; N, 3.70

Found: C, 82.67; H, 6.92; N, 3.50.

- 5 Examples 13-21 can be prepared from Example 11 Part A by the method in Example 11 Part D or Example 12 Part A.

Example 13



10

MS (Cl-NH_3 , + ions) m/e 370 ($M+H$).

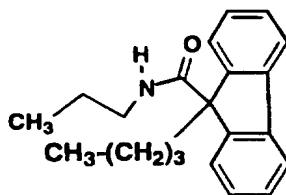
mp: $57-59^\circ$

Anal. Cald'd for $C_{26}H_{27}NO$:

15 C, 84.51; H, 7.36; N, 3.79

Found: C, 84.53; H, 7.41; N, 3.70.

Example 14



20

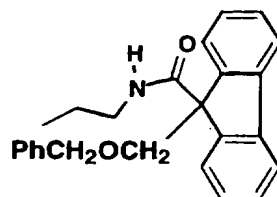
MS (Cl-NH_3 , + ions) m/e 308 ($M+H$).

mp: $60-62^\circ$

Anal. Cald'd for $C_{21}H_{25}NO + 0.05 \text{ mol } C_6H_{14}$:

25 C, 82.07; H, 8.32; N, 4.49

Found: C, 82.12; H, 8.76; N, 4.65.

Example 15

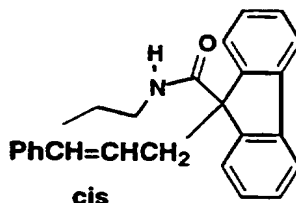
5 MS (Cl-NH₃, + ions) m/e 372 (M+H).

Anal. Cald'd for C₂₅H₂₅NO₂:

C, 80.83; H, 6.78; N, 3.77

Found: C, 80.48; H, 6.90; N, 3.71.

10

Example 16

MS (Cl-NH₃, + ions) m/e 368 (M+H).

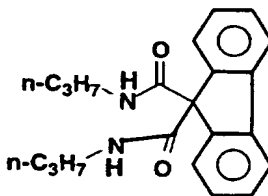
15 Anal. Cald'd for C₂₆H₂₅NO + 0.31 mol H₂O:

C, 83.71; H, 6.92; N, 3.75

Found: C, 83.84; H, 6.95; N, 3.62.

Example 17

20

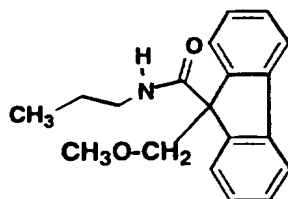


MS (Cl-NH₃, + ions) m/e 337 (M+H).

Anal. Cald'd for C₂₁H₂₄N₂O₂:

25 C, 74.97; H, 7.19; N, 8.33

Found: C, 74.94; H, 7.17; N, 7.80.

Example 18

5

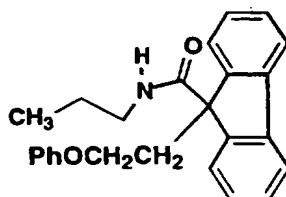
MS (Cl-NH₃, + ions) m/e 296 (M+H).

mp: 69-73°

Anal. Cald'd for C₁₉H₂₁NO₂ + 0.09 mol C₂₁H₂₅NO₃:

C, 76.98; H, 7.19; N, 4.68

10 Found: C, 76.71; H, 7.42; N, 4.65.

Example 19

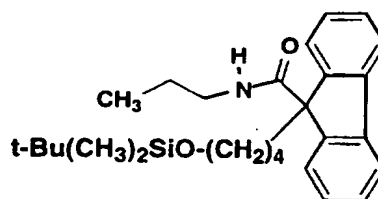
15

MS (Cl-NH₃, + ions) m/e 372 (M+H).Anal. Cald'd for C₂₅H₂₅NO₂ + 0.86 mol H₂O:

C, 77.60; H, 6.96; N, 3.62

Found: C, 77.92; H, 6.54; N, 3.88.

20

Example 20

5 MS (Cl-NH₃, + ions) m/e 438 (M+H).

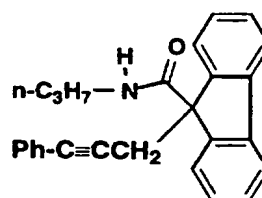
mp: 45-47°

Anal. Cald'd for C₂₇H₃₉NSiO₂:

C, 74.09; H, 8.98; N, 3.20

Found: C, 73.83; H, 9.34; N, 3.25.

10

Example 21

15 MS (ES, + ions) m/z 366 (M+H).

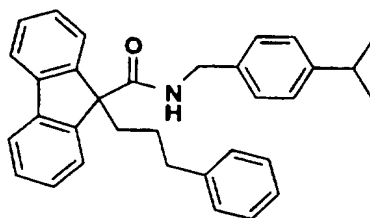
mp: 120-123°

Anal. Cald'd for C₂₆H₂₃NO + 0.15 mol H₂O:

C, 84.76; H, 6.38; N, 3.80

Found: C, 84.81; H, 6.29; N, 3.75.

20

Example 22

25

A. 9-(3-Phenylpropyl)-9H-fluorene-9-
carboxylic acid

To a solution of 10 g (48 mmol, 1 eq) of (9H)-fluorene-9-carboxylic acid in 200 mL of THF at 0°C was added 40 mL (100 mmol, 2.1 eq) of a 2.5 M solution of n-butyllithium in hexanes dropwise over 5 15 min. (First equivalent resulted in precipitation of Li salt of the carboxylate; solution became homogeneous as dianion formed.) The resulting green solution of dianion was stirred at 0°C for 10 min and 10.1 mL (66 mmol, 1.4 eq) of 10 1-bromo-3-phenylpropane was added quickly over 3 min. The reaction was stirred at 0°C and allowed to warm to RT as the ice bath melted. After 16 h, the basic reaction mixture (pH ~14) was extracted with water (1 x 200 mL, 2 x 50 mL). The combined 15 aqueous layers were acidified (to pH ~1) with 5 N HCl and extracted with ether (3 x 100 mL). The combined ether solutions were dried (MgSO₄), filtered and concentrated to afford 16.4 g of a viscous golden oil. Flash chromatography of the 20 oil on silica gel (250 g) eluted with 20% acetone in toluene containing 0.1 % acetic acid afforded 12.6 g of a yellow oil. The product was crystallized by slow evaporation of an ether/hexanes solution and then recrystallized from 25 ether/hexanes to afford 10.5 g (67%) of title compound as a white crystalline solid. m.p. 123-125°C.

TLC (silica gel, 10% MeOH in CH₂Cl₂, UV and I₂)
30 R_f = 0.67.

B. 9-(3-Phenylpropyl)-9H-fluorene-9-carboxylic acid, 4-nitrophenyl ester

To a solution of 10 g (30.4 mmol, 1 eq) of Part A compound in 100 mL of CH₂Cl₂ was added 100
5 μ L of DMF. The solution was cooled to 0°C and 22.8 mL (45.7 mmol, 1.5 eq) of a 2.0 M oxalyl chloride solution in CH₂Cl₂ was added over 5 min. The resulting bubbling solution was stirred at 0°C for 1.5 h (until bubbling had ceased). The solution
10 was concentrated and the residual oil was taken up in 50 mL of CH₂Cl₂ and reconcentrated. The resulting oil was dissolved in 150 mL of CH₂Cl₂ and 188 mg (1.5 mmol, 0.05 eq) of 4-dimethylaminopyridine was added. The solution was
15 cooled to 0°C and 5.1 mL (36.5 mmol, 1.2 eq) of triethylamine was added. To the resulting dark brown cloudy solution was added 12.7 g (91.3 mmol, 3 eq) of p-nitrophenol as a solid. Upon addition the reaction quickly became clear and the resulting
20 clear reaction mixture was allowed to warm to RT as the ice bath melted. (TLC indicated the reaction was essentially complete after 40 min.) After 15 h, the reaction was washed with 100 mL of ice-cold 1 N HCl. The organic solution was filtered through
25 cotton and concentrated to afford 24.84 g of a viscous golden-brown oil which was adsorbed onto silica gel (25 g) and chromatographed on silica gel (200 g) eluted with 10% ethyl acetate in hexanes to afford 13.54 g of a yellow solid. The solid was
30 further purified by recrystallization from ether/hexanes to provide 13.2 g (97%) of title compound as a pale yellow crystalline solid. m.p. 110-112°C.

TLC (silica gel, 25% EtOAc in hexanes, UV and I₂)

R_f = 0.39.

MS(CI, pos. ions): m/z 467 (M + NH₄), 450 (M + H).

5

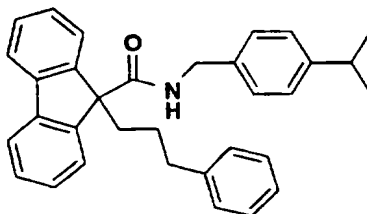
Anal. Calcd. for C₂₉H₂₃NO₄:

C, 77.49; H, 5.16; N, 3.12

Found: C, 77.27; H, 4.90; N, 2.99.

10

C.



The title compound was prepared via an automated procedure carried out on a Zymark Benchmate® Workstation using the following procedure.

The Benchmate® delivered 1 mL (80 mg, 0.18 mmol, 1 eq) of a stock solution of Part B compound in THF (80 mg/mL) to a 16 mm x 100 mm culture tube. The tube was removed and placed on a balance where 40 mg (0.27 mmol, 1.5 eq) of 4-isopropylbenzylamine was added manually by a Pipetman. The reaction was allowed to proceed until all reactions in the run were complete as indicated by disappearance of Part B compound by TLC (silica gel, 2% MeOH in CH₂Cl₂, R_f 0.88, visualized by UV and I₂).

The product was purified via solid phase extraction using a Varian SAX anion exchange column (1 g of sorbent, chloride form) on the Benchmate® by the procedure outlined below:

- 1) Syringe washed with 5 mL 300 mM KOH in MeOH.
- 2) Syringe washed with 5 mL 300 mM KOH in MeOH.
- 3) Column conditioned with 10 mL of 300 mM KOH(aq) in MeOH (0.25 mL/sec).
- 5 4) Column conditioned with 10 mL of MeOH (0.25 mL/sec).
- 5) Column conditioned with 10 mL of CH₂Cl₂ (0.25 mL/sec).
- 6) THF (1 mL) added to reaction mixture.
- 10 7) Reaction mixture loaded onto SAX column (0.05 mL/sec) and effluent collected into a second tube.
- 8) Column rinsed with 1 mL of THF and effluent collected into second tube.
- 15 9) Column rinsed with 2 mL of CH₂Cl₂ and effluent collected into second tube.
- 10) Syringe washed with 10 mL of CH₂Cl₂.
- 11) Syringe washed with 5 mL of MeOH.
- 12) Syringe washed with 4 mL of 300 mM KOH(aq) in MeOH.
- 20 13) Syringe washed with 4 mL of 300 mM KOH(aq) in MeOH.

25 This procedure was followed by a second solid phase extraction using a Varian SCX cation exchange column (500 mg of sorbent) on the Benchmate® by the procedure outlined below:

- 30 1) Column conditioned with 10 mL of CH₂Cl₂ (0.25 mL/sec).
- 2) Reaction mixture loaded onto SCX column (0.05 mL/sec) and effluent collected into product tube (tared).
- 35 3) Column rinsed with 2 mL of CH₂Cl₂ and effluent collected into product tube.

- 4) Syringe washed with 5 mL of CH₂Cl₂.
- 5) Syringe washed with 5 mL of CH₂Cl₂.

The product solution (approx. 5 mL) was concentrated using a speed vacuum for 14 h to afford 78 mg (94%) of title compound as a pale yellow oil.

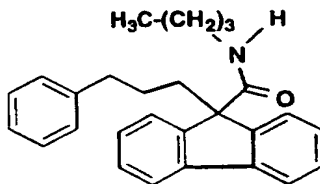
HPLC Purity = 94%; retention time = 9.5 minutes.
10 Column: YMC-Pack ODS 6.0 x 150 mm C18 with a 4 x 23 mm OSDA S-5 μ m guard column. Buffer: 10 mM KH₂PO₄ (pH 5.4, unadjusted). Elution: Isocratic at 85:15 buffer:acetonitrile for 5 minutes; linear gradient from 85:15 to 5:95 buffer:acetonitrile
15 over 9 minutes followed by isocratic 5:95 buffer:acetonitrile for 2 minutes with return to 85:15 buffer:acetonitrile over 2 minutes.

MS (CI, + ions): m/z 460 (M + H).
20

Example 23 to 58

Examples 23-58 can be prepared from Example 22 Part B compound by the method in Example 22, Part
25 C.

Example 23



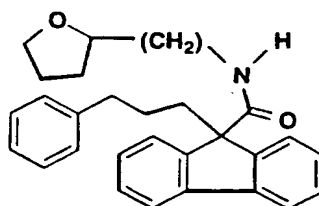
30 mp 73-75°C

MS (CI, pos. ions) 384 (M+H).

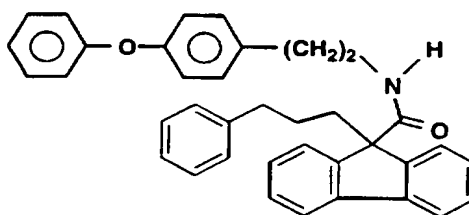
Anal. Cald'd for C₂₇H₂₉NO + 0.04 H₂O:

C, 84.40; H, 7.63; N, 3.65

Found: C, 84.02; H, 7.73; N, 3.66.

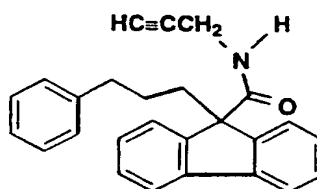
Example 24

5 MS (CI, pos. ions) 412 (M+H).

Example 25

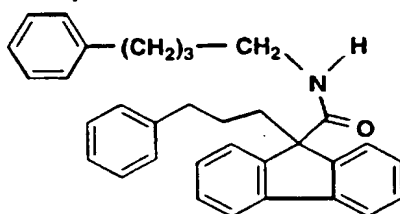
10

MS (CI, pos. ions) 524 (M+H).

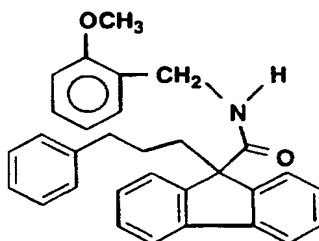
Example 26

15

MS (CI, pos. ions) 366 (M+H).

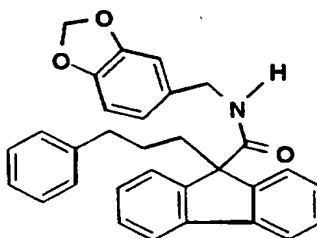
Example 27

5 MS (CI, pos. ions) 460 (M+H).

Example 28

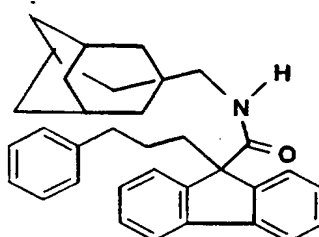
10

MS (CI, pos. ions) 448 (M+H).

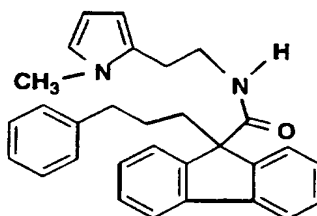
Example 29

15

MS (electrospray, pos. ions) 462 (M+H).

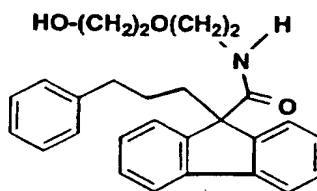
Example 30

5 MS (electrospray, pos. ions) 476 (M+H).

Example 31

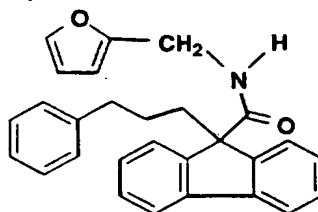
10

MS (electrospray, pos. ions) 435 (M+H).

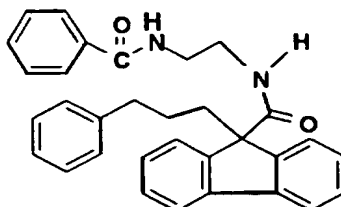
Example 32

15

MS (electrospray, pos. ions) 416 (M+H).

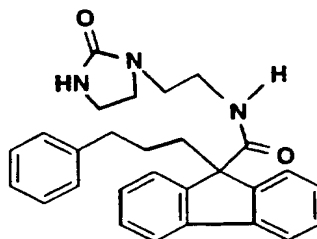
Example 33

5 MS (electrospray, pos. ions) 408 (M+H).

Example 34

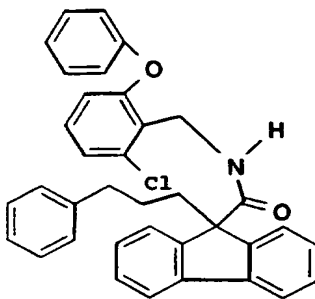
10

MS (electrospray, pos. ions) 475 (M+H).

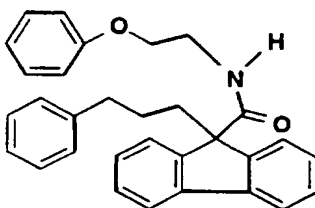
Example 35

15

MS (electrospray, pos. ions) 440 (M+H).

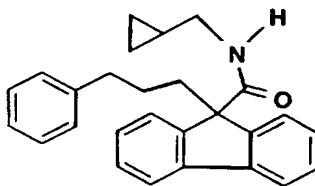
Example 36

5 MS (electrospray, pos. ions) 544 (M+H).

Example 37

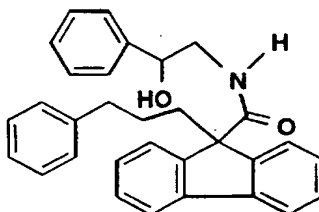
10

MS (electrospray, pos. ions) 448 (M+H).

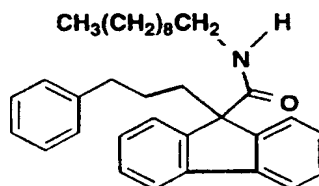
Example 38

15

MS (electrospray, pos. ions) 382 (M+H).

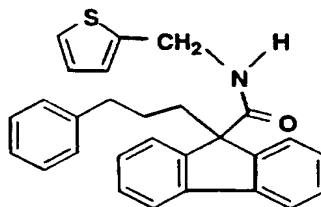
Example 39

5 MS (electrospray, pos. ions) 448 (M+H).

Example 40

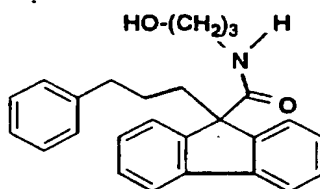
10

MS (electrospray, pos. ions) 468 (M+H).

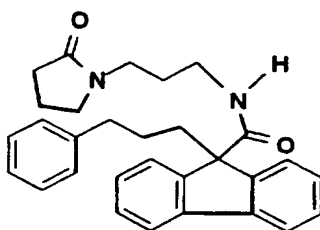
Example 41

15

MS (electrospray, pos. ions) 424 (M+H).

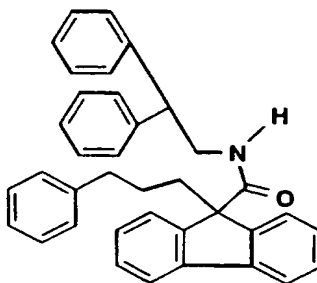
Example 42

5 MS (electrospray, pos. ions) 386 (M+H).

Example 43

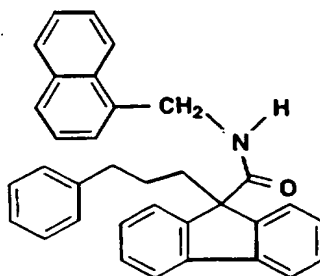
10

MS (electrospray, pos. ions) 453 (M+H).

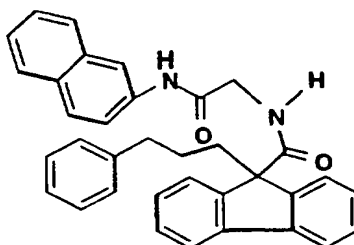
Example 44

15

MS (electrospray, pos. ions) 508 (M+H).

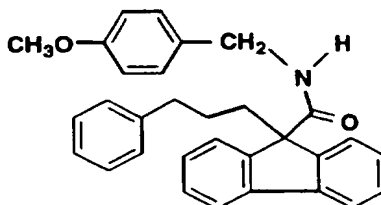
Example 45

5 MS (electrospray, pos. ions) 468 (M+H).

Example 46

10

MS (electrospray, pos. ions) 511 (M+H).

Example 47

15

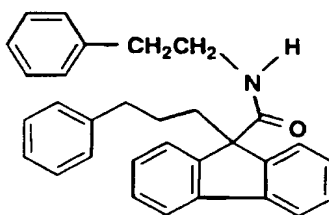
M.P. 105-107°C

MS (CI, + ions) m/z 448

Anal. Calcd'd for C₃₁H₂₉NO₂ + 0.15 H₂O:

C, 82.69; H, 6.56; N, 3.11

20 Found: C, 82.36; H, 6.37; N, 2.99.

Example 48

M.P. 104-105°C

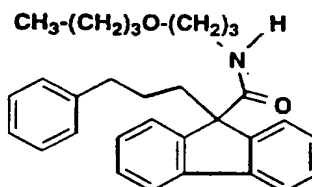
5 MS (Cl, + ions) m/z 432

Anal. Cald'd for C₃₁H₂₉NO:

C, 86.27; H, 6.77; N, 3.25

Found: C, 85.87; H, 6.60; N, 3.14.

10

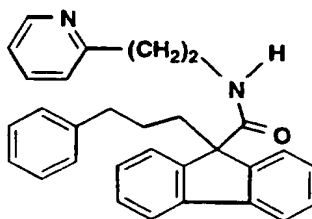
Example 49

MS (Cl, + ions) m/z 442

15 Anal. Cald'd for C₃₀H₃₅NO₂:

C, 81.59; H, 7.99; N, 3.17

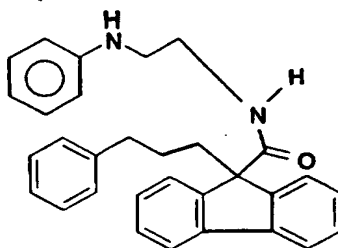
Found: C, 81.93; H, 8.11; N, 3.04.

Example 50

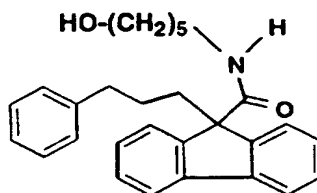
20

MS (electrospray, pos. ions) 433 (M+H)

25

Example 51

5 MS (electrospray, pos. ions) 447 (M+H)

Example 52

10

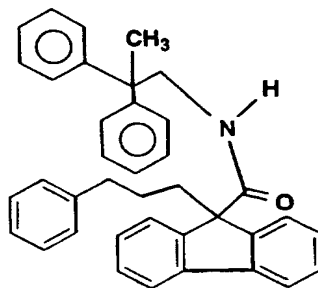
MS (Cl₂, + ions) m/z 414 (M+H)

Anal. Calcd'd for C₂₈H₃₁NO₂ + 0.1 CH₂Cl₂:

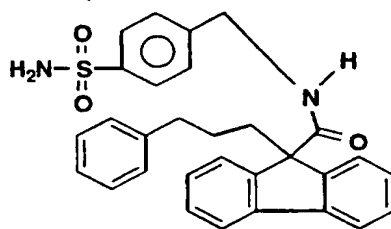
C, 79.97; H, 7.45; N, 3.32

Found: C, 80.29; H, 7.57; N, 3.27.

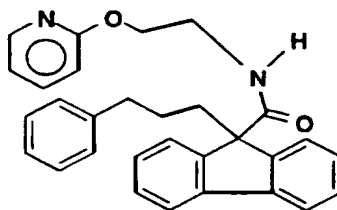
15

Example 53

20 MS (electrospray, pos. ions) 458 (M+H)

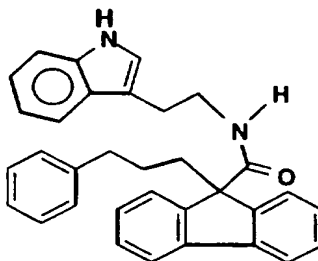
Example 54

5 MS (electrospray, pos. ions) 497

Example 55

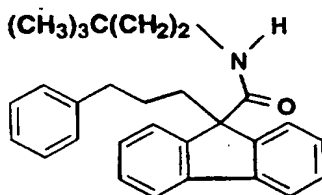
10

MS (electrospray, pos. ions) 449 (M+H)

Example 56

15

MS (electrospray, pos. ions) 471 (M+H)

Example 57

5 MS (electrospray, pos. ions) 412 (M+H)

Example 58

9-(3-Phenylpropyl)-N-(2,2,2-trifluoroethyl)-9H-
fluorene-9-carboxamide

10

A solution of oxalyl chloride in dichloromethane (1 mL, 2.0 mmol) was added to a stirred suspension of Example 22 Part A compound (0.30 g 0.90 mmol) in 5 mL of dichloromethane. The
15 reaction mass was treated with 1 drop of DMF, allowed to stir for 2 h and concentrated. The remainder was diluted with 10 mL of THF, cooled to -40° and treated with 2,2,2-trifluoroethylamine (0.44 g, 7.5 mmol) and warmed to RT over 3 h. The
20 reaction mixture was diluted with 20 mL of water and 50 mL of ethyl acetate. The organic fraction was extracted with 15 mL of 1 M KOH, dried (MgSO₄) and concentrated. The remainder was purified by column chromatography on silica gel (50 g) with
25 hexanes (100 mL) followed by 2:8 ethyl acetate/hexane (300 mL) to give 0.28 g (88%) of title compound as a white solid. The resulting solid was recrystallized from 1.5 mL of a 10:1 ethanol/water solution to give 0.19 g (52%) of
30 title compound as needles. mp 86-88°C.

TLC Silica gel (3:7 ethyl acetate/hexane) R_f = 0.7.

Mass Spec. (ES, + ions) m/z 410 (M+H).

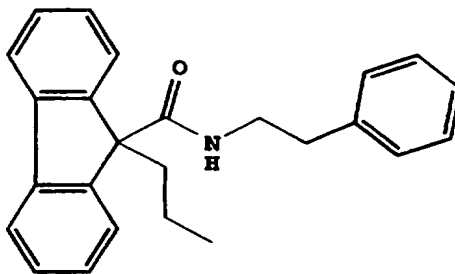
Anal. Calc'd for $C_{25}H_{22}NOF_3$

C, 73.34; H, 5.42; N, 3.42

Found: C, 72.98; H, 4.94; N, 3.35.

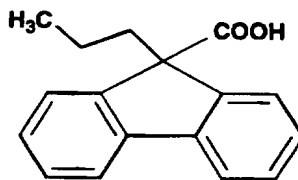
5

Example 59



10

A.



A solution of (9H)-9-fluorene-9-carboxylic acid (12 g, 57 mmol) in 250 ml of THF was cooled to 0°C under an argon atmosphere and 2 equiv. (71.25 ml) of a 1.6 M n-butyl lithium solution in hexane was added followed by the addition of n-propyl iodide (7.5 ml, 13.1 g, 77 mmol). The reaction mixture was stirred at 0°C for 6 hrs. TLC, silica, MeOH:CH₂Cl₂ (1:9) showed starting acid still present, therefore, an additional 1 ml of n-propyl iodide was added and the reaction stirred for 4 hrs at 0°C. The reaction was quenched by adding 75 ml of water and the pH was adjusted to pH 1 with 3 N HCl. The reaction mixture was extracted with hexane (3x200ml) and the hexane extract washed with water, brine and dried over anhydrous sodium sulfate. The solvents were evaporated yielding the crude product as a yellow oil which was dissolved in ~250

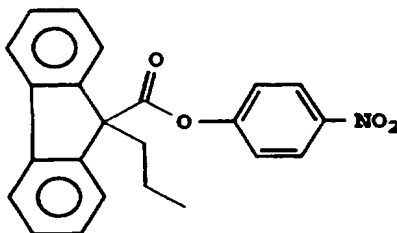
ml of ethanol and heated at reflux with Darco G-60, filtered through Celite and concentrated to approximately one half of the original volume. Water was slowly added until the mixture became
5 cloudy. The mixture was reheated and slowly allowed to cool to room temperature yielding 10.5 grams (73%) of title compound as colorless crystals. m.p. 120-122°C.

10 Anal Calc'd for $C_{17}H_{16}O_2$ (MW 252.3):

C, 80.93; H, 6.39

Found: C, 81.01; H, 6.22.

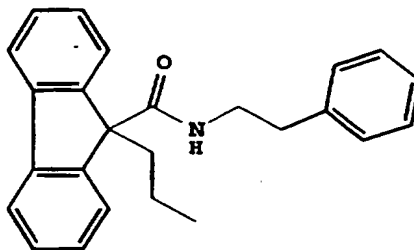
B.



15

Example 59 Part B was prepared analogously to Example 22 Part B starting with Example 59 Part A (1.5 g, 5.95 mmol), 4.5 mL (8.92 mmol) of oxalyl
20 chloride, 6 drops (catalytic) of dimethylformamide, 2.5 g (17.8 mmol) of 4-nitrophenol, and 1 mL (7.14 mmol) of triethylamine.

C.



Example 59 compound was prepared via an automated procedure carried out on a Zymark Benchmate® Workstation using the following procedure.

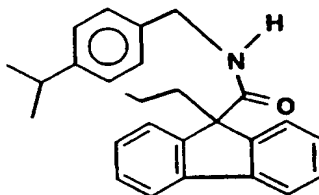
The Benchmate® delivered 1 mL (44 mg, 0.11 mmol, 1 eq) of a stock solution of Example 59 Part B in THF (44 mg/mL) to a 16 mm x 100 mm culture tube. The tube was removed and placed on a balance where phenethyl amine (24 mg, 0.17 mmol) was added manually. The reaction was allowed to proceed until all reactions in the run were complete as indicated by disappearance of Example 59 Part B compound by TLC (silica gel, 2% MeOH in CH₂Cl₂, visualized by UV and I₂).

The product was purified in an analogous manner to Example 22, Part C, to give title compound as a colorless solid in 81% yield. MS (electrospray, + ions) m/z 356 (M+H).

Examples 60 to 84

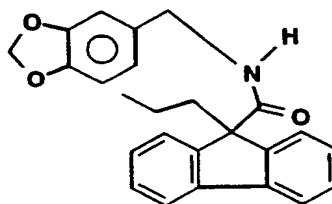
Examples 60-84 can be prepared from Example 59 Part B compound by the method in Example 59 Part C.

5

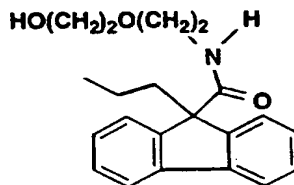
Example 60

MS (electrospray, pos. ions) 384 (M+H)

10

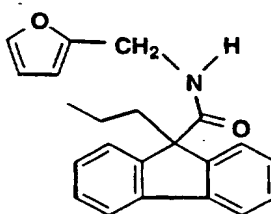
Example 61

15 MS (electrospray, pos. ions) 386 (M+H)

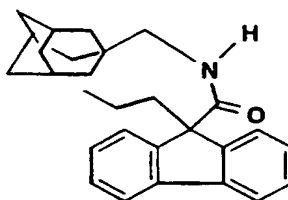
Example 62

20

MS (electrospray, pos. ions) 340 (M+H)

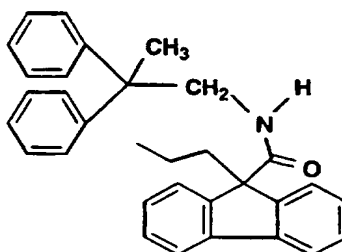
Example 63

5 MS (electrospray, pos. ions) 399 (M+H)

Example 64

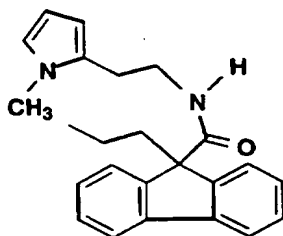
10

MS (electrospray, pos. ions) 400 (M+H)

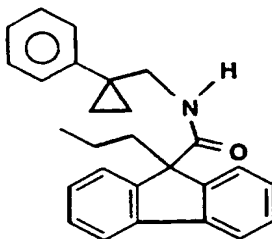
Example 65

15

MS (electrospray, pos. ions) 446 (M+H)

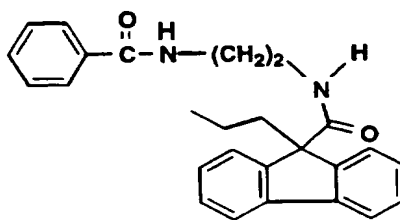
Example 66

5 MS (electrospray, pos. ions) 359 (M+H)

Example 67

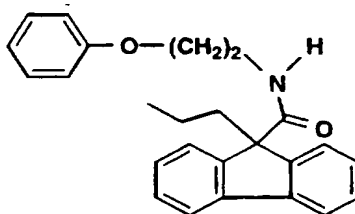
10

MS (electrospray, pos. ions) 382 (M+H)

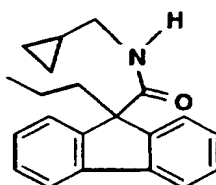
Example 68

15

MS (electrospray, pos. ions) 399 (M+H)

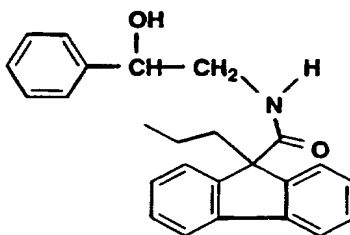
Example 69

5 MS (electrospray, pos. ions) 372 (M+H)

Example 70

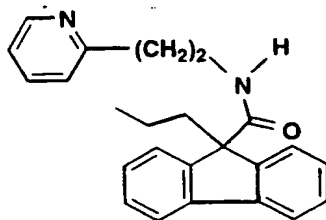
10

MS (electrospray, pos. ions) 306 (M+H)

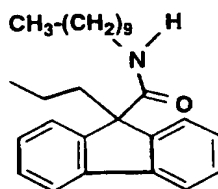
Example 71

15

MS (electrospray, pos. ions) 372 (M+H)

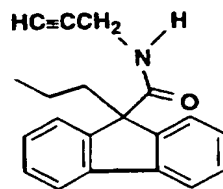
Example 72

5 MS (electrospray, pos. ions) 357 (M+H)

Example 73

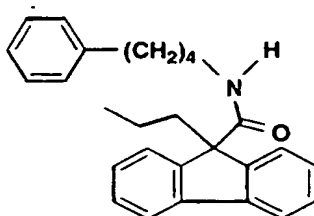
10

MS (electrospray, pos. ions) 392 (M+H)

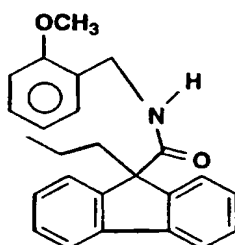
Example 74

15

MS (electrospray, pos. ions) 291 (M+H)

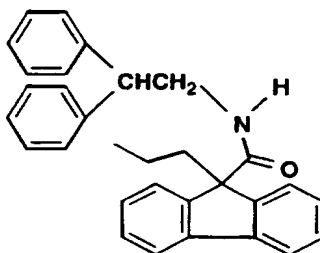
Example 75

5 MS (electrospray, pos. ions) 384 (M+H)

Example 76

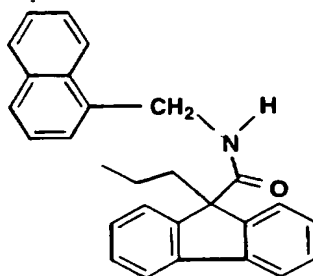
10

MS (electrospray, pos. ions) 372 (M+H)

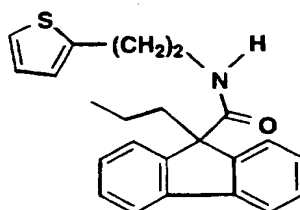
Example 77

15

MS (electrospray, pos. ions) 432 (M+H)

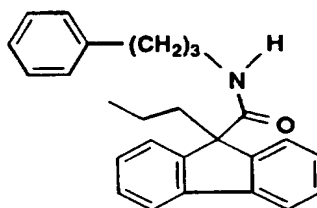
Example 78

5 MS (electrospray, pos. ions) 392 (M+H)

Example 79

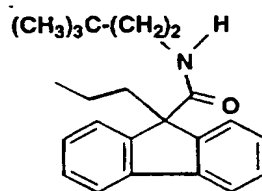
10

MS (electrospray, pos. ions) 362 (M+H)

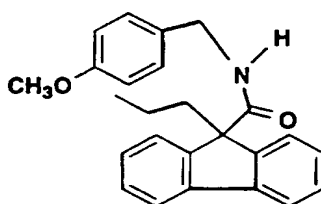
Example 80

15

MS (electrospray, pos. ions) 370 (M+H)

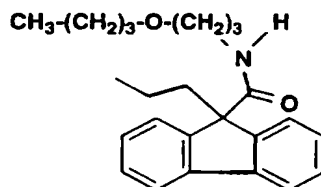
Example 81

5 MS (electrospray, pos. ions) 336 (M+H)

Example 82

10

MS (electrospray, pos. ions) 372 (M+H)

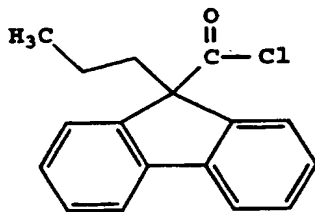
Example 83

15

MS (electrospray, pos. ions) 366 (M+H)

Example 84N-Methyl-N-(phenylmethyl)-9-propyl-9H-fluorene-9-carboxamide

A.



5

A solution of Example 59 Part A compound (2.02 g, 8 mmol) in 15 ml of dry dichloromethane was cooled to 0°C under an argon atmosphere. N,N-Dimethylformamide (50µl) was added to the reaction mixture followed by the addition of oxalyl chloride (0.77 ml, 1.12 g, 8.8 mmol) over a 10 minute period. After stirring for 15 min at 0°C the reaction was allowed to warm to room temperature and stir for 1 hr. The volatiles were removed under vacuum and the oily residue was redissolved several times in dichloro-methane and evaporated yielding the title acid chloride as a colorless solid which was used without any further purification.

20

B. N-Methyl-N-(phenylmethyl)-9-propyl-9H-fluorene-9-carboxamide

A solution of Example 84 Part A compound (1 mmol) in 8 ml of dry THF was cooled to 0°C under an argon atmosphere and 2.1 equiv. of N-methyl-N-benzylamine (255 mg, 2.1 mmol) was added. After stirring at ambient temperature for 2 hrs. the reaction was diluted with 25 ml of ethyl acetate and washed with sat. sodium bicarbonate solution. The ethyl acetate extract was washed with sodium bicarbonate, water, brine and dried over anhydrous sodium sulfate. The crude product was purified by flash chromatography on Merck EM silica gel eluting

with 5% EtOAc/hexane yielding 186 mg (53%) of pure title product as a colorless solid. m.p. 73-74°C.

Anal Calc'd for C₂₅H₂₅NO (FW 355.48):

5 C, 84.47; H, 7.09; N, 3.94

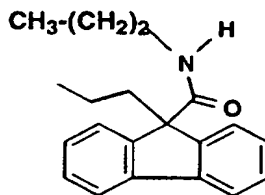
Found: C, 84.57; H, 7.16; N, 3.90.

Examples 85 to 92

Examples 85 to 92 can be prepared from

10 Example 84 Part A compound by the method in Example 84, Part B.

Example 85



15

M.P. 96-98°C

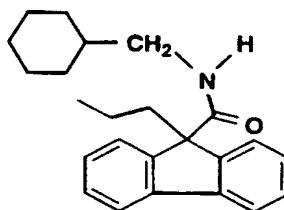
Mass Spec. (CI) (M+H)⁺=308⁺

Anal. Cald'd for C₂₁H₂₅NO:

C, 82.04; H, 8.20; N, 4.56

20 Found: C, 82.06; H, 8.46; N, 4.48.

Example 86



25 M.P. 106-107°C

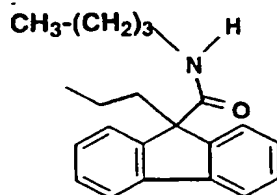
Mass Spec. (CI) (M+H)⁺=348

Anal. Cald'd for C₂₄H₂₉NO:

C, 82.95; H, 8.41; N, 4.03

Found: C, 82.71; H, 8.22; N, 3.82.

30

Example 87

M.P. 60-62°C

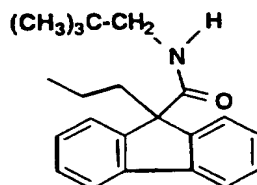
5 Mass Spec. (CI) (M+H)=308

Anal. Cald'd for C₂₁H₂₅NO:

C, 82.04; H, 8.20; N, 4.56

Found: C, 82.09; H, 8.35; N, 4.42.

10

Example 88

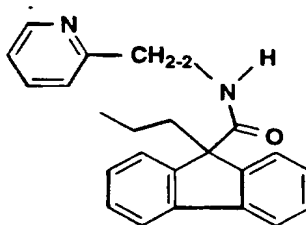
M.P. 62-64°C

Mass Spec. (CI) (M+H) = 322

15 Anal. Cald'd for C₂₂H₂₇NO:

C, 82.20; H, 8.47; N, 4.36

Found: C, 81.86; H, 8.19; N, 4.41.

Example 89

M.P. 102-103°C

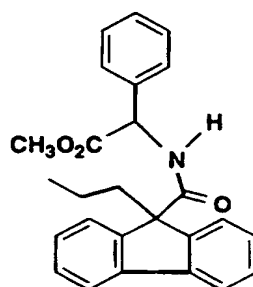
5 Mass Spec. (CI) (M+H) = 343

Anal. Cald'd for C₂₃H₂₂N₂O:

C, 80.67; H, 6.48; N, 8.18

Found: C, 80.51; H, 6.46; N, 8.04.

10

Example 90

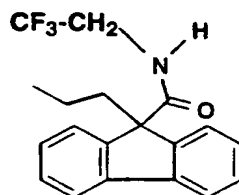
Mass Spec. (CI) (M+H) = 400

15 Anal. Cald'd for C₂₆H₂₅NO₃ + 0.1 H₂O:

C, 77.87; H, 6.33; N, 3.49

Found: C, 77.87; H, 6.35; N, 3.53.

20

Example 91

M.P. 113-115°C

MS (CI, + ions) m/z 334 (M+H)

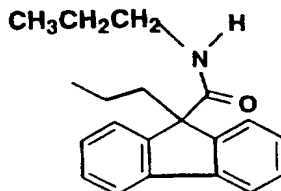
Anal. Cald'd for $C_{19}H_{18}NOF_3$:

C, 68.46; H, 5.44; N, 4.20; F, 17.10

Found: C, 68.24; H, 5.70; N, 4.18; F, 17.22.

5

Example 92



M.P. 75-77°C

MS (CI, + ions) m/z 294 (M+H)

10 Anal. Cald'd for $C_{20}H_{23}NO$:

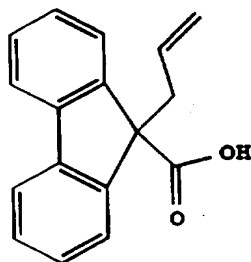
C, 81.87; H, 7.90; N, 4.77

Found: C, 81.88; H, 8.18; N, 4.70.

Example 93

15 9-(2-Propenyl)-N-(2-pyridinylmethyl)-9H-fluorene-9-carboxamide

A.



- 20 To a methoxyethanol solution (100 ml) of 9H-fluorene-9-carboxylic acid (10.83 g, 0.0515 mol) under argon was added solid KOH (6.8 g, 0.103 mol). After about 15 min the KOH had dissolved resulting in a blue-green colored solution. Allyl
- 25 bromide (8.9 ml, 0.526 mol) was then added and stirred at room temperature for 2 h. The reaction mixture was partitioned between EtOAc/H₂O and the aqueous layer extracted twice with EtOAc. The aqueous layer was brought to pH 2 with 1N HCl,

extracted twice with EtOAc, and the combined organics were dried over Na₂SO₄. Evaporation in vacuo gave 11.63 g of a brown colored oily-solid. The residue was co-evaporated with CH₂Cl₂, Et₂O, 5 EtOAc, and hexanes to give an orange colored solid 9.19 g (70% recovery). A portion of the material (400 mg) was purified by flash chromatography (twice, 3x13 cm), eluting with 3%MeOH:CH₂Cl₂ to give title compound as a colorless solid (160 mg). 10 m.p. 128-130°C.

MS: (CI, M+NH₄⁺): m/z 268.

Anal. Calc. for C₁₇H₁₄O₂ · 0.13 H₂O:

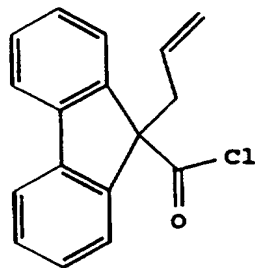
15 C, 80.80; H, 5.69

Found: C, 80.80; H, 5.61.

Alternative Preparation of Part A Compound

20 To a THF (15 ml) suspension of 9-fluorene carboxylic acid (5.28 g, 0.025 mol) at 0°C under argon was added sodium hexamethyldisilazane (50 mL, 0.05 mol, 1M in THF), initial solid formation, and the final greenish-brown solution stirred for 5 25 min.. Allyl bromide (2.3 mL, 0.0265 mol) was added and after 1 h the mixture was poured into cold water. The aqueous layer was extracted with EtOAc and the organic layer washed with water. The combined aqueous layers were brought to pH 1 with 30 3N HCl and extracted with EtOAc. The organics were washed with brine, dried over Na₂SO₄, and the volatiles removed in vacuo to give an oily-solid residue (6.96 g). The residue was crystallized from EtOH/water to give 2.81 g colorless solid. After 35 concentrating the mother liquor, a second crop (1.04 g) and third crop (0.5 g) were obtained of Part A compound (4.35 g, 69% yield). mp 128-130°C.

B.



5 To a CH₂Cl₂ (40 ml) solution of Part A
compound (3.83 g, 0.015 mol) at 0°C under argon was
added oxalyl chloride (2 ml, 0.023 mol) then DMF
(90 µL). After 15 min. at 0°C and 1.5 h at room
temperature, the volatiles were removed in vacuo
10 and the residue co-evaporated with CH₂Cl₂ to give
title compound, which was used directly.

C. 9-(2-Propenyl)-N-(2-pyridinylmethyl)-
9H-fluorene-9-carboxamide

15 To a THF (35 ml) solution of Part B acid
chloride (0.015 mol) at -5°C under argon was added
2-(aminomethyl)pyridine (3.4 mL, 0.033 mol), with
extra THF (10 mL) added to improve stirring. After
15 min, the mixture was brought to room temperature
20 for 4 h. At 0°C, the reaction mixture was quenched
with saturated NaHCO₃, the aqueous layer extracted
3 times with EtOAc, the combined organic layers
were washed with H₂O, brine and dried over Na₂SO₄.
The volatiles were removed in vacuo to give a
25 colored solid (5.1 g). The residue was purified by
flash column chromatography (SiO₂, 10 by 20 cm),
eluting with 2.5% MeOH:CH₂Cl₂, to give title
compound (2.67 g, 51% yield) as a colorless solid.
m.p. 110-111°C.

30

MS: (CI, (M+H)⁺): 341 m/z.

Anal. Calc. for $C_{23}H_{20}N_2O$:

C, 81.15; H, 5.92; N, 8.23

Found: C, 80.95; H, 5.99; N, 8.21.

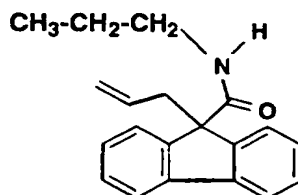
5

Examples 94 to 102

Example 94 to 102 can be prepared from
Example 93 Part B compound by the method in Example
93 Part C.

10

Example 94



mp 85.5-86.5°C

MS (CI, $(M+H)^+$) m/z 292

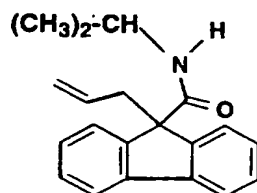
15 Anal. Cald'd for $C_{20}H_{21}NO$:

C, 82.44; H, 7.26; N, 4.81

Found: C, 82.31; H, 7.44; N, 4.77.

Example 95

20



mp 74-75.5°C

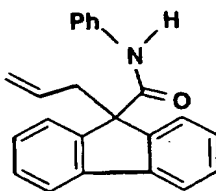
MS (CI, $(M+H)^+$) m/z 292

Anal. Cald'd for $C_{20}H_{21}NO \cdot 0.09 H_2O$:

25

C, 81.98; H, 7.29; N, 4.78

Found: C, 82.02; H, 7.33; N, 4.74.

Example 96

mp 112.5-114°C

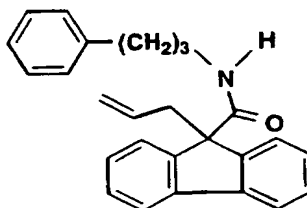
5 MS (CI, (M+H)⁺) m/z 326

Anal. Cald'd for C₂₃H₁₉NO•0.12 H₂O:

C, 84.32; H, 5.92; N, 4.27

Found: C, 84.35; H, 5.76; N, 4.24.

10

Example 97

mp 74.5-75.5°C

MS (CI, (M+H)⁺) m/z 368

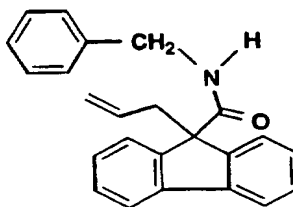
15 Anal. Cald'd for C₂₆H₂₅NO•0.13 H₂O:

C, 84.42; H, 6.88; N, 3.79

Found: C, 84.48; H, 6.84; N, 3.73.

Example 98

20



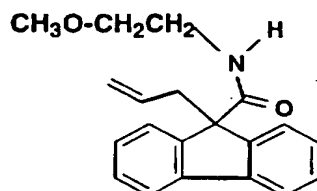
mp 80.5-81.5°C

MS (CI, (M+H)⁺) m/z 340

Anal. Cald'd for C₂₄H₂₁NO:

25 C, 84.92; H, 6.24; N, 4.13

Found: C, 84.58; H, 6.15; N, 4.10.

Example 99

5 mp 87-88.5°C

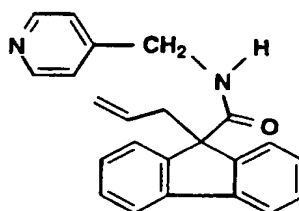
MS (CI, (M+H)⁺) m/z 308

Anal. Cald'd for C₂₀H₂₁NO₂:

C, 78.15; H, 6.89; N, 4.56

Found: C, 78.05; H, 6.83; N, 4.47.

10

Example 100

mp 127-128°C

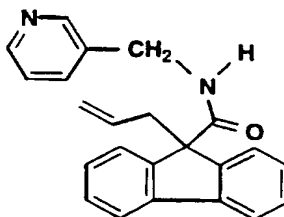
15 MS (CI, (M+H)⁺) m/z 341

Anal. Cald'd for C₂₃H₂₀N₂O:

C, 81.15; H, 5.92; N, 8.23

Found: C, 81.27; H, 5.88; N, 8.11.

20

Example 101

mp 68-71°C

MS (CI, (M+H)⁺) m/z 341

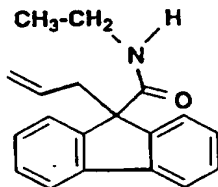
Anal. Cald'd for $C_{23}H_{20}N_2O$:

C, 81.15; H, 5.92; N, 8.23

Found: C, 81.11; H, 5.86; N, 8.12.

5

Example 102



mp 87.5-88.5°C

Anal. Cald'd for $C_{19}H_{19}NO \cdot 0.13 H_2O$:

10

C, 81.57; H, 6.94; N, 5.01

Found: C, 81.58; H, 6.79; N, 5.00.

Example 103

15 9-(1-Piperidinylcarbonyl)-9-(2-propenyl)-9H-fluorene

To a 0°C suspension under argon of Example 93 Part A compound (0.495 g, 1.98 mmol), piperidine (0.39 ml, 3.94 mmol), hydroxybenzotriazole hydrate (0.40 g, 2.96 mmol), and N-methylmorpholine (0.22 ml, 2.00 mmol) in DMF (6 ml) was added EDCI (0.44 g, 2.27 mmol) and the reaction was allowed to come to room temperature overnight. After 24 h, the reaction was quenched with saturated $NaHCO_3$, the aqueous layer extracted twice with EtOAc, and the combined organics dried over Na_2SO_4 overnight. The volatiles were removed in vacuo to give an oil (600 mg). The residue was purified by flash column chromatography (SiO_2 , 3 by 17 cm), eluting with CH_2Cl_2 to give title compound (0.265 g, 42% yield) as a colorless solid. m.p. 64-66°C.

MS: (CI, + ions): m/z 318 (M+H).

Anal. Calc. for C₂₂H₂₃NO:

C, 83.24; H, 7.30; N, 4.41

Found: C, 83.25; H, 7.32; N, 4.36.

5

Example 104

N-Butyl-9-(2-propenyl)-9H-fluorene-9-carboxamide

To a CH₂Cl₂ (8 ml) and pyridine (0.28 ml) solution of Example 93 Part A compound (400 mg, 1.60 mmol) under argon was added cyanuric fluoride (0.27 mL, 3.20 mmol). After 1.5 h, the cloudy reaction mixture was partitioned between ice-water and CH₂Cl₂. The organics were dried over Na₂SO₄, and the volatiles removed in vacuo to give an oily-solid residue (420 mg). The crude residue was used directly in the subsequent reaction.

To a THF (7 ml) solution of the above crude residue (1.5 mmol) at 0°C under argon was added n-butylamine (0.3 mL, 3.04 mmol) and the reaction brought to room temperature. After 16 h, the mixture was quenched with saturated NaHCO₃, the aqueous layer extracted 2 times with EtOAc, and the combined organic layers were washed with brine and dried over Na₂SO₄. The volatiles were removed in vacuo to give an oily-solid (470 mg). The residue was purified by flash column chromatography (SiO₂, 5 by 6 cm), eluting with 12.5% EtOAc:hexanes, to give title compound (362 mg, 79% yield) as a colorless solid. m.p. 62.5-64°C.

30

MS: (CI, M+H⁺): m/z 306.

Anal. Calc. for C₂₁H₂₃NO:

C, 82.59; H, 7.59; N, 4.59

Found: C, 82.72; H, 7.45; N, 4.46.

35

Example 105

9-[[2,2-Bis(trifluoromethyl)-1,3-dioxolan-4-yl]-
methyl-N-ethyl-9H-fluorene-9-carboxamide

5 To a CH₂Cl₂ (0.5 ml) solution of Example
102 compound (35 mg, 0.125 mmol) and
hexafluoroacetone hydrate (40 mg, 0.207 mmol) was
added 30% H₂O₂ (25 µl). After several hours, MgSO₄
was added and the reaction stirred for 24 h, when a
10 second amount of the ketone and 30% H₂O₂ were
added. After 48 h total, the reaction was quenched
with aqueous sodium thiosulfate and sat. NaHCO₃.
The aqueous layer was extracted twice with CH₂Cl₂
and the combined organics were dried over Na₂SO₄.
15 The organics were concentrated in vacuo and the
residue was purified by flash column chromatography
(SiO₂, 2 by 6 cm), eluting with 1% EtOAc: CH₂Cl₂,
to give title compound (20 mg, 34% yield) as a
colorless solid. m.p. 91-93°C.

20

MS: (CI, M+H⁺): m/z 460.

Anal. Calc. for C₂₂H₁₉F₆NO₃:

C, 57.52; H, 4.17; N, 3.05

25 Found: C, 57.51; H, 4.00; N, 2.93.

Example 106

9-(2,3-Dihydroxypropyl)-N-ethyl-9H-fluorene-9-
carboxamide

30

To an acetone:H₂O (4 ml, 9:1) suspension of
Example 102 compound (191 mg, 0.689 mmol) and N-
methyilmorpholine-N-oxide (215 mg, 1.59 mmol) under
argon was added OsO₄ (several small crystals).
35 After stirring at room temperature overnight, the
reaction was cooled and then quenched with aq.
sodium metabisulfite. The reaction mixture was

stirred 15 min. and the aqueous layer extracted twice with EtOAc. The organics were washed with brine, dried over Na₂SO₄, and concentrated to an oil (220 mg). The residue was purified by flash column chromatography (SiO₂, 3 by 9 cm), eluting with 4:1 EtOAc:CH₂Cl₂, to give title compound (106 mg, 49% yield) as a colorless, hygroscopic foam.

MS: (CI, M+H⁺): m/z 312.

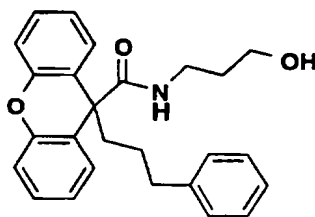
Anal. Calc. for C₁₉H₂₁NO₃ • 0.4 H₂O:

C, 71.64; H, 6.90; N, 4.40

Found: C, 71.68; H, 6.84; N, 4.36.

Example 107

9-(3-Phenylpropyl)-N-(3-hydroxy)propyl-9H-xanthene-9-carboxamide



A. 9-(3-Phenylpropyl)-9H-xanthene-9-carboxylic acid

To a solution of 10 g (44 mmol, 1 eq) of 9-xanthenylcarboxylic acid in 200 mL of THF at 0°C was added 37.2 mL (93 mmol, 2.1 eq) of a 2.5 M solution of n-butyllithium in hexanes dropwise over 15 min. (First equivalent resulted in precipitation of Li salt of the carboxylate; solution became homogeneous as dianion formed.) The resulting orange solution of dianion was stirred at 0°C for 10 min and 9.4 mL (62 mmol, 1.4 eq) of 1-bromo-3-phenylpropane was added quickly over 3 min. The reaction was stirred at 0°C and allowed to warm to RT as the ice bath melted.

After 16 h, the basic reaction mixture (pH ~14) was extracted with water (3 x 100 mL). The combined aqueous layers were acidified (to pH ~1) with 6 N HCl and extracted with ether (3 x 100 mL). The combined ether solutions were dried (MgSO₄), filtered and concentrated to afford 17.04 g of a viscous golden oil. The oil was dissolved in hot hexanes using a small amount of CH₂Cl₂ to effect complete dissolution. Concentration of this solution resulted in a yellow solid which was recrystallized from ether/hexanes to afford 13.3 g (88%) of title compound as a white crystalline solid, m.p. 137-138°C.

TLC (silica gel, 10% MeOH in CH₂Cl₂, UV and I₂)
R_f = 0.52.

B. 9-(3-Phenylpropyl)-9H-xanthene-9-carboxylic acid, 4-nitrophenyl ester

To a solution of 10 g (29.0 mmol, 1 eq) of Part A compound in 100 mL of CH₂Cl₂ was added 100 µL of DMF. The solution was cooled to 0°C and 22.0 mL (43.6 mmol, 1.5 eq) of a 2.0 M oxalyl chloride solution in CH₂Cl₂ was added over 5 min. The resulting bubbling solution was stirred at 0°C for 1.5 h (until bubbling had ceased). The solution was concentrated and the residual oil was taken up in 50 mL of CH₂Cl₂ and re-concentrated. The resulting oil was dissolved in 150 mL of CH₂Cl₂ and 188 mg (1.52 mmol, 0.05 eq) of 4-dimethylamino-pyridine was added. The solution was cooled to 0°C and 4.9 mL (34.8 mmol, 1.2 eq) of triethylamine was added. To the resulting dark brown cloudy solution was added 12.1 g (87.1 mmol, 3 eq) of p-nitrophenol as a solid. Upon addition the reaction quickly became clear and the resulting clear reaction

mixture was allowed to warm to RT as the ice bath melted. (TLC indicated the reaction was essentially complete after 40 min.) After 15 h, the reaction was washed with 100 mL of ice-cold 1 N HCl. The organic solution was filtered through cotton and concentrated to afford 24.22 g of a viscous golden-brown oil which was chromatographed on silica gel (200 g) eluted with 25% hexanes in CH₂Cl₂ to afford 13.45 g of a viscous golden oil. The product was crystallized by concentrating down a ether/hexane solution and the crude solid was then recrystallized from ether/hexanes to afford 11.8 g (87%) of title compound as an off-white crystalline solid, m.p. 93-94°C. TLC (silica gel, 25% EtOAc in hexanes, UV and I₂) R_f = 0.39.

MS(CI, pos. ions): m/z 483 (M + NH₄), 466 (M + H).

Anal. Calcd. for C₂₉H₂₃NO₅:

C, 74.83; H, 4.98; N, 3.01

Found: C, 74.61; H, 4.71; N, 2.88.

C. 9-(3-Phenylpropyl)-N-(3-hydroxy)propyl-9H-xanthene-9-carboxamide

The title compound was prepared via an automated procedure carried out on a Zymark Benchmate® Workstation using the following procedure.

The Benchmate® delivered 1 mL (80 mg, 0.18 mmol, 1 eq) of a stock solution of title compound in THF (80 mg/mL) to a 16 mm x 100 mm culture tube. The tube was removed and placed on a balance where 3-amino-1-propanol (24 mg, 0.27 mmol) was added manually. The reaction was allowed to proceed

until all reactions in the run were complete as indicated by disappearance of title compound by TLC (silica gel, 2% MeOH in CH₂Cl₂, visualized by UV and I₂).

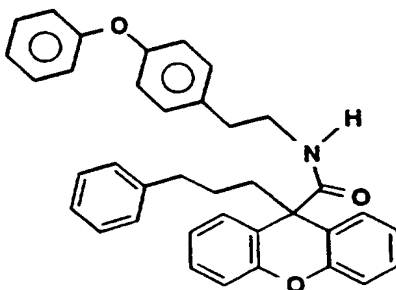
- 5 The product was purified in an analogous manner to Example 22, Part C, to give title compound as a pale oil (55 mg) in 69% yield. MS (electrospray, pos. ions) = 402 (M+H).

10

Examples 108-140

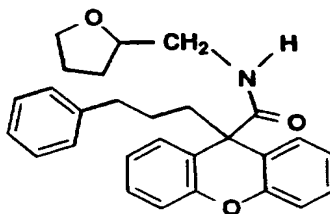
Examples 108 to 140 can be prepared from Example 107 Part B compound by the method in Example 107, Part C.

15

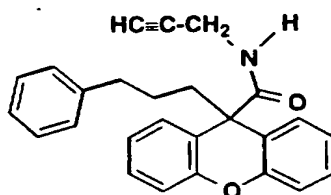
Example 108

MS (CI, pos. ions) 540 (M+H)

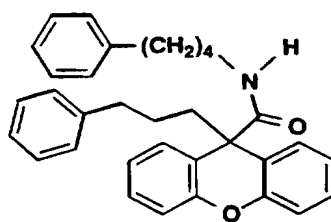
20

Example 109

25 MS (CI, pos. ions) 428 (M+H)

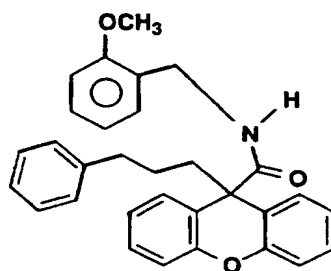
Example 110

5 MS (CI, pos. ions) 382 (M+H)

Example 111

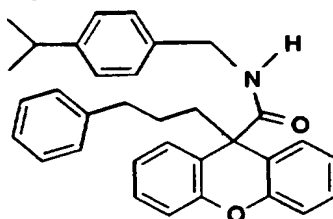
10

MS (CI, pos. ions) 476 (M+H)

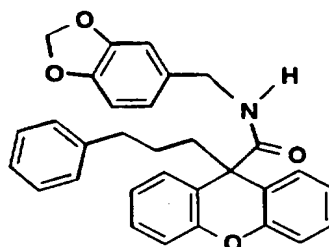
Example 112

15

MS (CI, pos. ions) 464 (M+H)

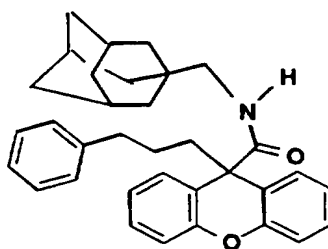
Example 113

5 MS (CI, pos. ions) 476 (M+H).

Example 114

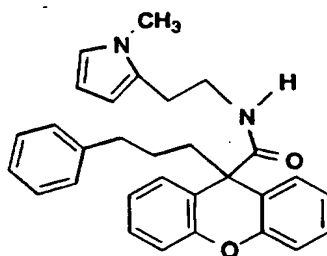
10

MS (electrospray, pos. ions) 478 (M+H).

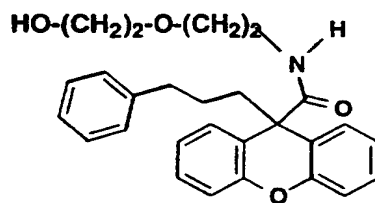
Example 115

15

MS (electrospray, pos. ions) 492 (M+H).

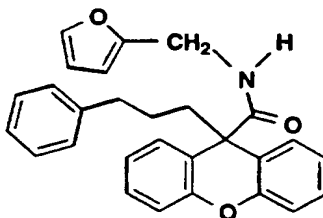
Example 116

5 MS (electrospray, pos. ions) 451 (M+H).

Example 117

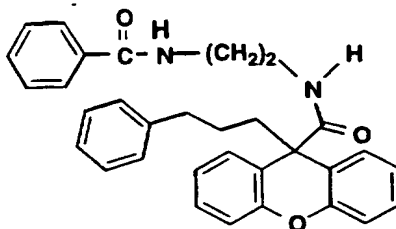
10

MS (electrospray, pos. ions) 432 (M+H).

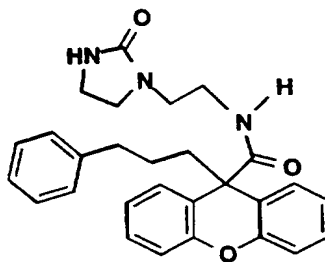
Example 118

15

MS (electrospray, pos. ions) 424 (M+H).

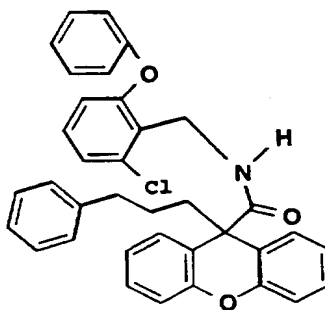
Example 119

5 MS (electrospray, pos. ions) 491 (M+H).

Example 120

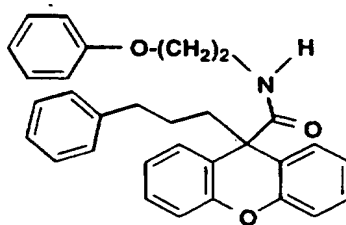
10

MS (electrospray, pos. ions) 456 (M+H).

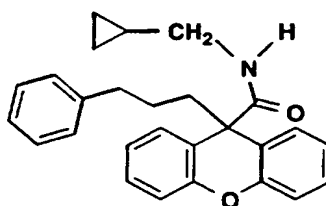
Example 121

15

MS (electrospray, pos. ions) 560 (M+H).

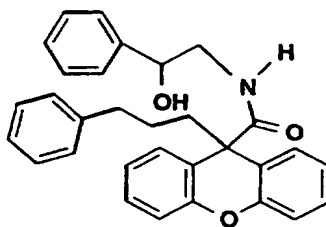
Example 122

5 MS (electrospray, pos. ions) 464 (M+H).

Example 123

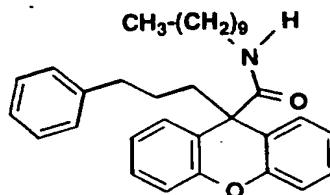
10

MS (electrospray, pos. ions) 398 (M+H).

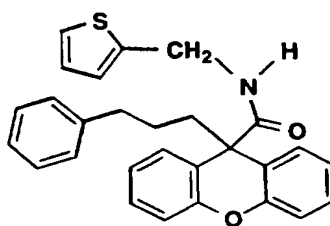
Example 124

15

MS (electrospray, pos. ions) 464 (M+H).

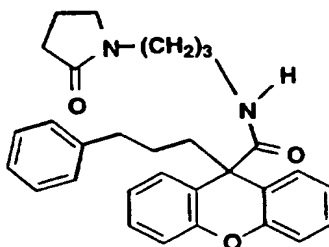
Example 125

5 MS (electrospray, pos. ions) 484 (M+H).

Example 126

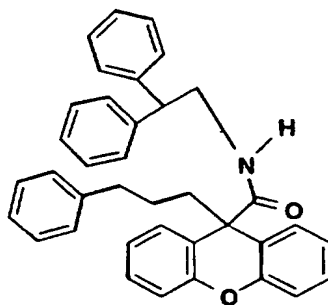
10

MS (electrospray, pos. ions) 440 (M+H).

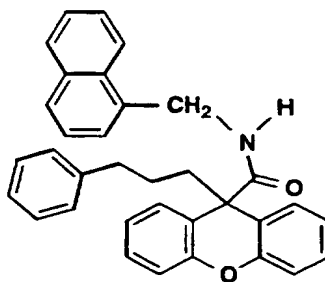
Example 127

15

MS (electrospray, pos. ions) 469 (M+H).

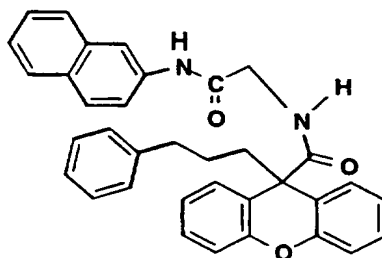
Example 128

5 MS (electrospray, pos. ions) 524 (M+H).

Example 129

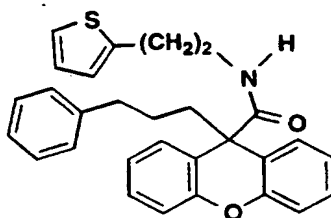
10

MS (electrospray, pos. ions) 484 (M+H).

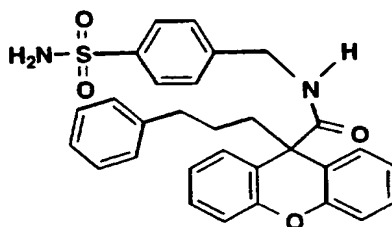
Example 130

15

MS (electrospray, pos. ions) 527 (M+H).

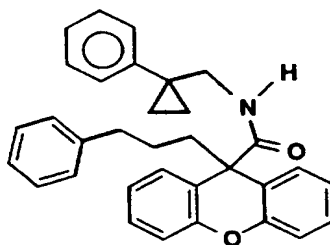
Example 131

5 MS (electrospray, pos. ions) 454 (M+H).

Example 132

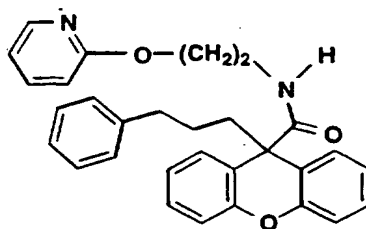
10

MS (electrospray, pos. ions) 513 (M+H).

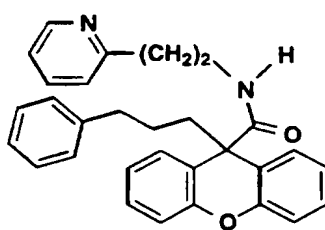
Example 133

15

MS (electrospray, pos. ions) 474 (M+H).

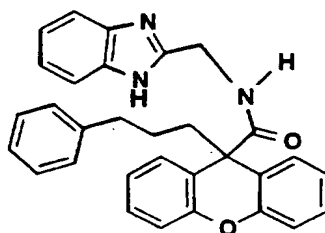
Example 134

5 MS (electrospray, pos. ions) 465 (M+H).

Example 135

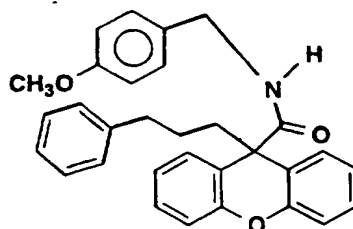
10

MS (electrospray, pos. ions) 449 (M+H).

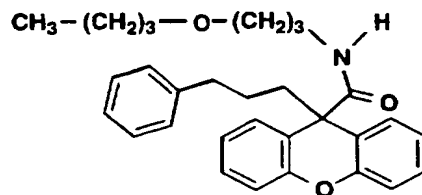
Example 136

15

MS (electrospray, pos. ions) 474 (M+H).

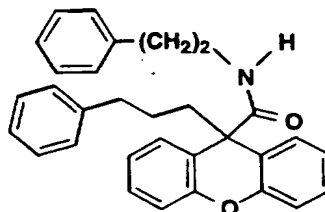
Example 137

5 MS (electrospray, pos. ions) 464 (M+H).

Example 138

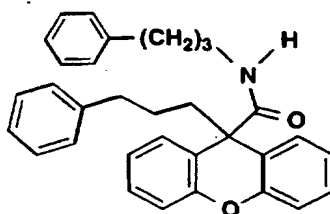
10

MS (electrospray, pos. ions) 458 (M+H).

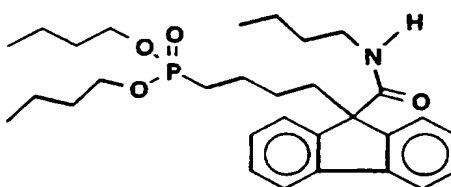
Example 139

15

MS (electrospray, pos. ions) 448 (M+H).

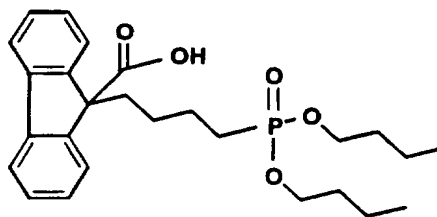
Example 140

5 MS (electrospray, pos. ions) 462 (M+H).

Example 141

10

A.



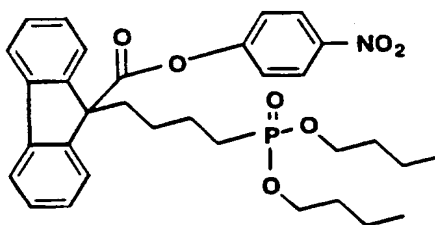
To a suspension of fluorene-(9H)-9-
 15 carboxylic acid (0.45 g, 2.18 mmol) in THF (5 mL)
 at -78°C was added n-butyllithium in hexanes (1.70
 mL, 4.20 mmol) dropwise at such a rate to maintain
 the internal temperature below -40°C. The
 resulting bright yellow solution was stirred at
 20 -40°C for 0.5 h and treated with compound Example
 11, Part B (0.60 g, 1.82 mmol). The mixture was
 slowly warmed to room temperature and stirred for 6
 h when the mixture was treated with 0.1 g (10 mol%)
 of tetrabutylammonium iodide and allowed to stir
 25 overnight. The mixture was diluted with 0.1N HCl
 (25 mL, 2.50 mmol) and ethyl acetate (50 mL). The
 layers were separated, the organic fraction dried

(Na₂SO₄) and concentrated to give 1 g of crude oil. This material could be purified by flash chromatography (silica gel, eluting with 5% MeOH:ethyl acetate) and crystallization from hexane/ethyl acetate/methylene chloride to gave title compound
5 as a colorless solid. mp 123-125°C.

TLC Silica gel (3:7:1 acetone/dichloromethane/acetic acid) R_f = 0.45.

10

B.

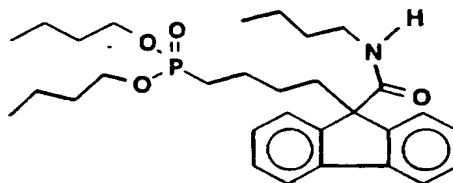


Part B compound was prepared as described
15 for Example 22 Part B compound, using 7.59 g (16.5 mmol) of Example 144 Part A compound, 12.4 mL (24.9 mmol) of oxalyl chloride, 100 µL (catalytic) of dimethyl-formamide, 101 mg (0.8 mmol) of 4-dimethylamino-pyridine, 2.01 g (19.8 mmol) of triethylamine, and 6.91 g (49.6 mmol) of 4-nitrophenol in CH₂Cl₂ (ml). The crude product was purified by flash chromatography on silica gel (400 g) eluted with methylene chloride (3 L), followed by 2% methanol in methylene chloride. The
20 product was further purified flash chromatography on silica gel (150 g) eluted with 7:3 hexanes:ethyl acetate (3 L) followed by 6:4 hexanes:ethyl acetate (3 L), to provide 6.29 g (73%) of title compound, as a pale yellow oil.

30

TLC Silica gel (9:1 toluene:acetone, visualization by UV, I₂) R_f = 0.27.

C.



- A solution of 104 mg (0.18 mmol) of Part B compound in 1 mL of THF was treated with 20 mg (0.36 mmol) of n-butylamine for 16 hours. The product was purified via solid phase extraction using a Varian SAX anion exchange column (1 g of sorbent, chloride form) by the procedure outlined below:
- 1) Column conditioned with 10 mL of 300 mM KOH(aq) in MeOH.
 - 2) Column conditioned with 10 mL of MeOH.
 - 15 3) Column conditioned with 10 mL of CH₂Cl₂.
 - 4) Reaction mixture loaded onto SAX column and effluent collected into a product tube.
 - 5) Column rinsed with 1 mL of THF and effluent collected into product tube.
 - 20 6) Column rinsed with 2 mL of CH₂Cl₂ and effluent collected into product tube.

This procedure was followed by a second solid phase extraction using a Varian SCX cation exchange column (1 mg of sorbent) by the procedure outlined below:

- 1) Column conditioned with 10 mL of CH₂Cl₂.
- 2) Reaction mixture loaded onto SCX column and effluent collected into product tube (tared).
- 30 3) Column rinsed with 2 mL of CH₂Cl₂ and effluent collected into product tube.

The product solution (approx. 5 mL) was concentrated using a speed vac for 14 h to afford 59 mg (63%) of title compound as a clear oil.

- 5 HPLC Purity = 90%; retention time = 13.0 minutes.
Column: EM Lichrosphere C8 Select-B 250 mm.
Solvent A: 10% methanol:90% water:0.2% H₃PO₄.
Solvent B: 90% methanol:10% water:0.2% H₃PO₄.
Elution: Linear gradient from 30:70 A:B over 10
10 minutes followed by isocratic 100%B for 10 minutes.

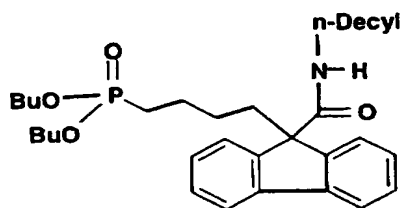
MS (Electrospray, + ions): m/z 598 (M + H).

Examples 142 to 185

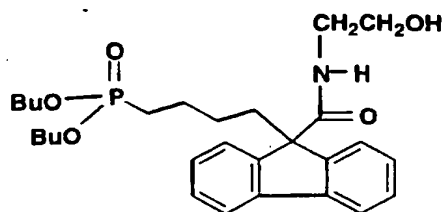
- 15 Examples 142 to 175 can be prepared from Example 141 Part B compound by the method in Example 141 Part C. For examples where the starting amine is a salt, the amine was free based by partitioning between THF and aqueous saturated
20 sodium bicarbonate or by adding an equimolar amount of triethylamine.
Note, Bu stands for n-butyl.

Example 142

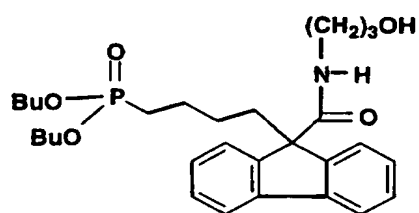
25



MS (ES, + ions) m/z 598 (M+H).

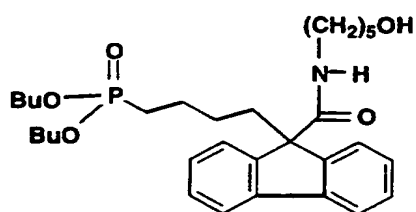
Example 143

5 MS (ES, + ions) 501 (M+H).

Example 144

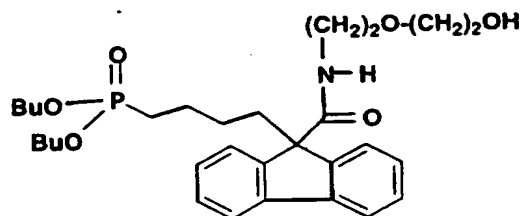
10

MS (ES, + ions) 516 (M+H).

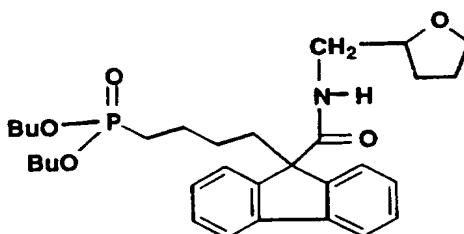
Example 145

15

MS (ES, + ions) 544 (M+H).

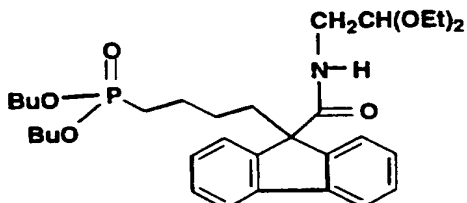
Example 146

5 MS (ES, + ions) 546 (M+H).

Example 147

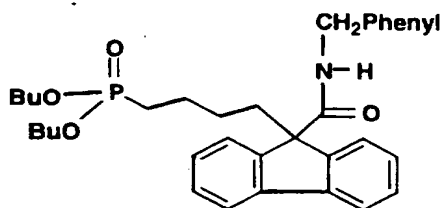
10

MS (ES, + ions) 542 (M+H).

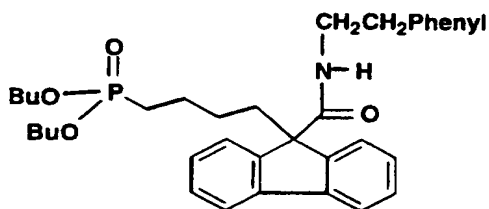
Example 148

15

MS (ES, + ions) 596 (M+Na).

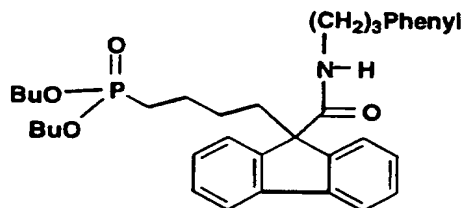
Example 149

5 MS (ES, + ions) 548 (M+H).

Example 150

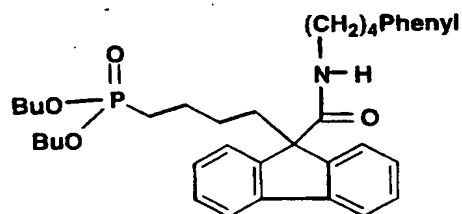
10

MS (ES, + ions) 562 (M+H).

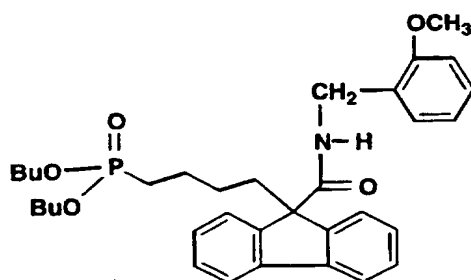
Example 151

15

MS (ES, + ions) 576 (M+H).

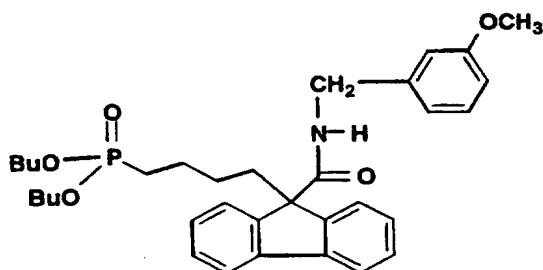
Example 152

5 MS (ES, + ions) 590 (M+H).

Example 153

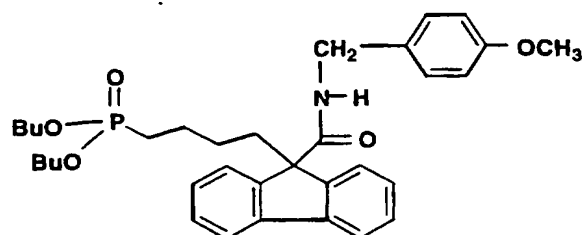
10

MS (ES, + ions) 578 (M+H).

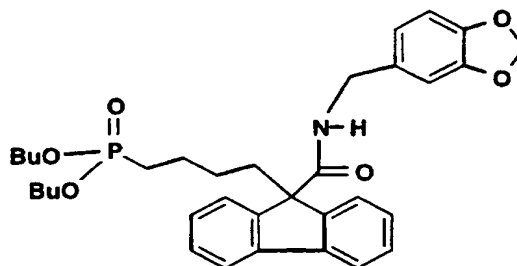
Example 154

15

MS (ES, + ions) 578 (M+H).

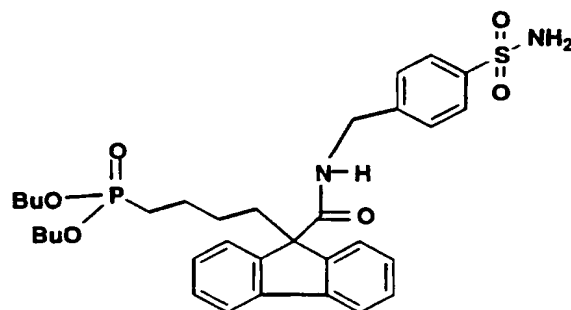
Example 155

5 MS (ES, + ions) 578 (M+H).

Example 156

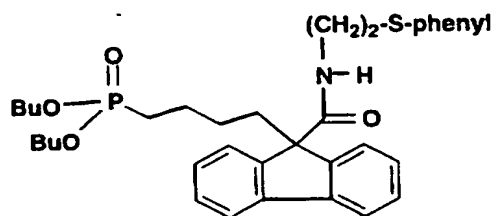
10

MS (ES, + ions) 592 (M+H).

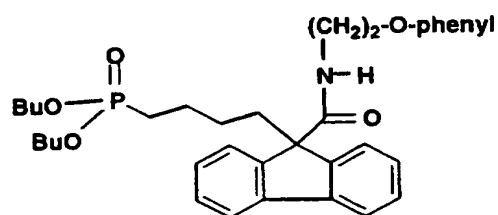
Example 157

15

MS (ES, + ions) 627 (M+H).

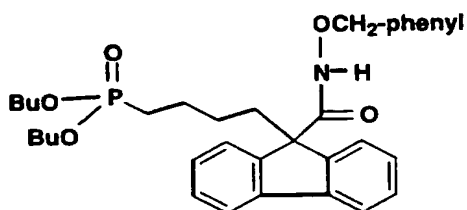
Example 158

5 MS (ES, + ions) 594 (M+H).

Example 159

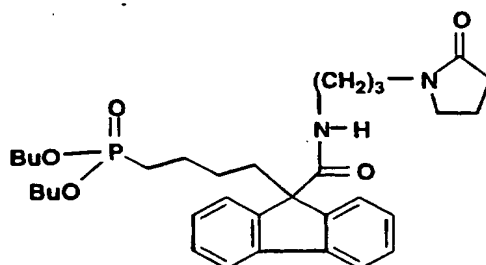
10

MS (ES, + ions) 578 (M+H).

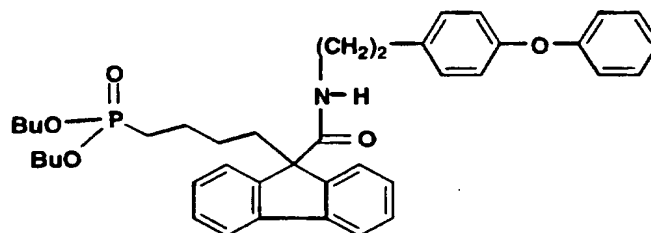
Example 160

15

MS (ES, + ions) 564 (M+H).

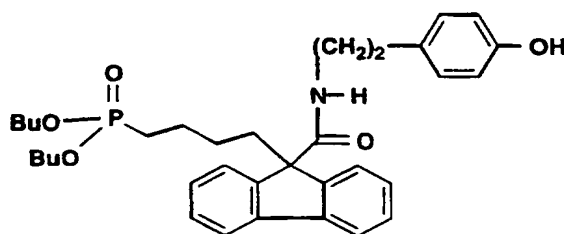
Example 161

5 MS (ES, + ions) m/z 583 (M+H).

Example 162

10

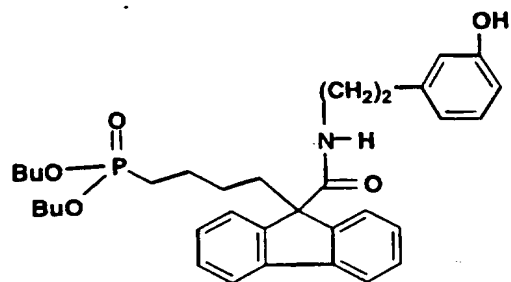
MS (ES, + ions) 654 (M+H).

Example 163

15

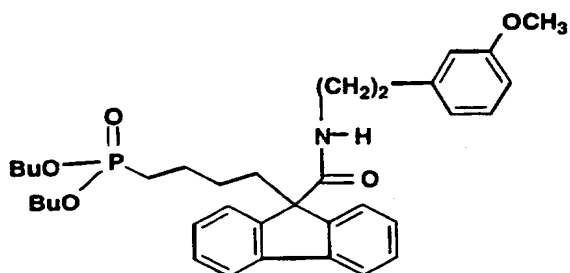
MS (ES, + ions) 578 (M+H).

Example 164



5 MS (ES, + ions) 578 (M+H).

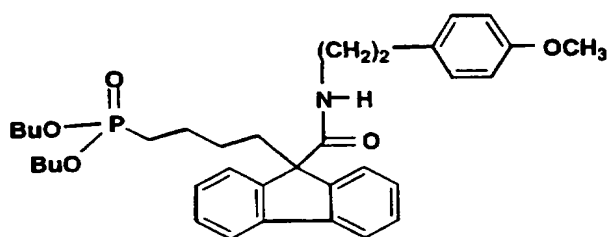
Example 165



10

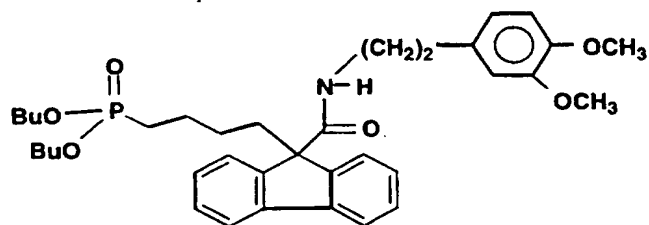
MS (ES, + ions) 592 (M+H).

Example 166

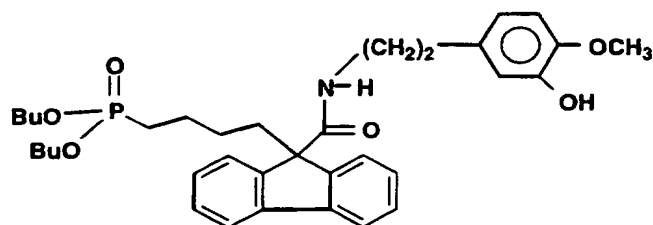


15

MS (ES, + ions) 592 (M+H).

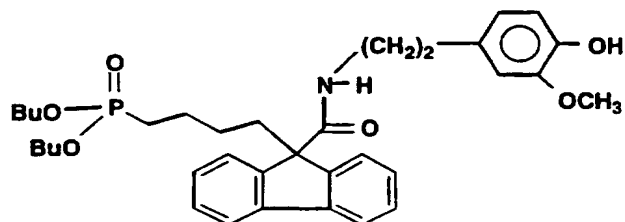
Example 167

5 MS (ES, + ions) 622 (M+H).

Example 168

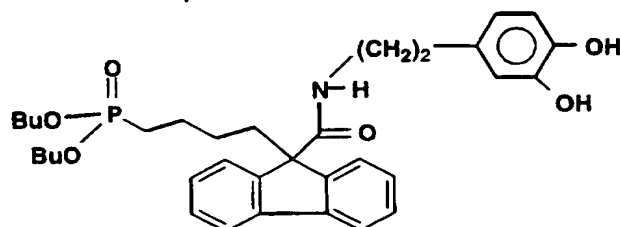
10

MS (ES, + ions) 608 (M+H).

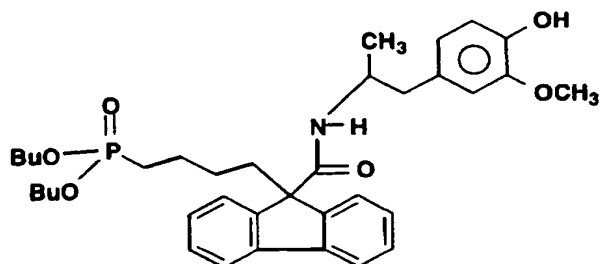
Example 169

15

MS (ES, + ions) 608 (M+H).

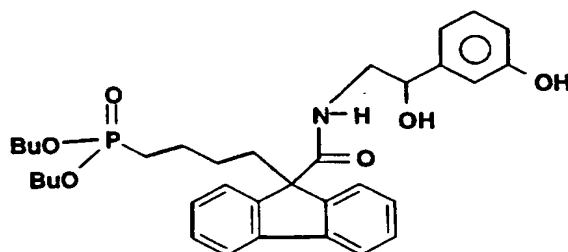
Example 170

5 MS (ES, + ions) 594 (M+H).

Example 171

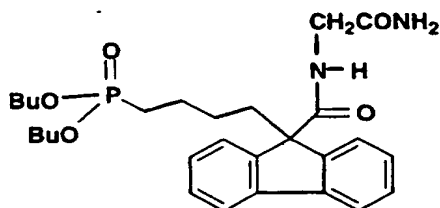
10

MS (ES, + ions) 622 (M+H).

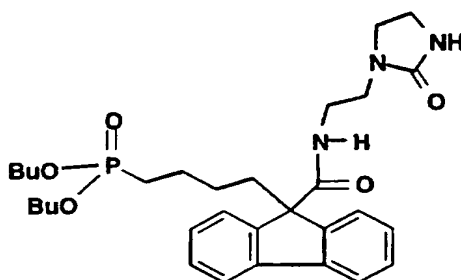
Example 172

15

MS (ES, + ions) 594 (M+H).

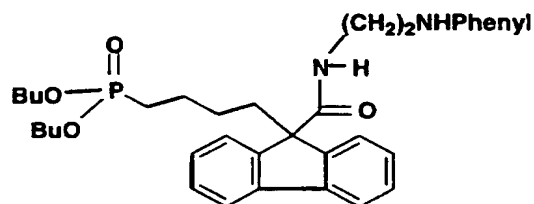
Example 173

5 MS (ES, + ions) 515 (M+H).

Example 174

10

MS (ES, + ions) 570 (M+H).

Example 175

15

A solution of 104 mg (0.18 mmol) of Example 141 Part B compound in 1 mL of THF was treated with 22 mg (0.16 mmol, 0.9 eq) of N-phenethylaminediamine for 48 hours. The product was purified via solid phase extraction using a Varian SCX anion exchange column (1 g of sorbent, 0.6 meq/g) by the procedure outlined below:

20

- 1) Column conditioned with 10 mL of CH_2Cl_2 (0.25 mL/sec).
- 2) Reaction mixture loaded onto SCX column (0.05 mL/sec).
- 5 3) Column rinsed with 10 mL of methanol.
- 4) Column rinsed with 4 mL of 1M NH_3 /methanol and effluent collected into product tube.
- 5) Syringe washed with 2 mL of methanol.

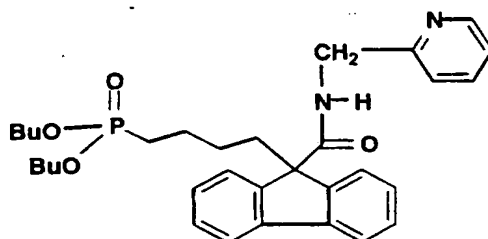
10 This procedure was followed by a second solid phase extraction using a Varian SAX cation exchange column (1 g of sorbent, 0.7 meq/g) on the Benchmate® by the procedure outlined below:

- 15 1) Syringe washed with 4 mL of methanol.
- 2) Column conditioned with 10 mL of CH_2Cl_2 (0.25 mL/sec).
- 3) Product solution from SCX column loaded onto SAX
- 20 column (0.05 mL/sec) and effluent collected into product tube (tared).
- 4) Column rinsed with 2 mL of CH_2Cl_2 and effluent collected into product tube.
- 25 5) Syringe washed with 4 mL of methanol.

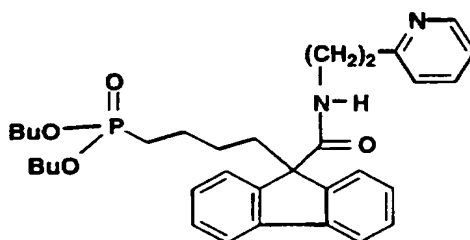
30 The product solution (approx. 5 mL) was concentrated using a speed vac for 14 h to afford 66 mg (72%) of the title compound as a yellow semi-solid.

MS (Electrospray, + ions): m/z 577 (M + H).

35 Examples 176 to 185 can be prepared from Example 141 Part B compound by the method in Example 175.

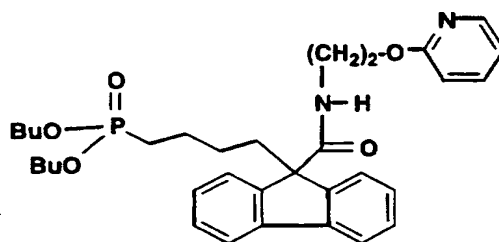
Example 176

5 MS (ES, + ions) 549 (M+H).

Example 177

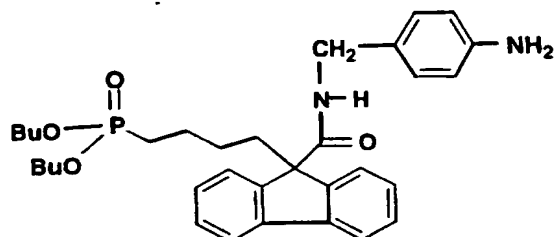
10

MS (ES, + ions) 563 (M+H).

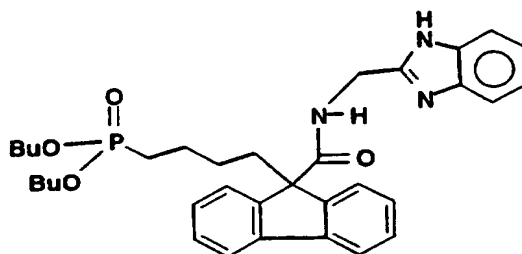
Example 178

15

MS (ES, + ions) 579 (M+H).

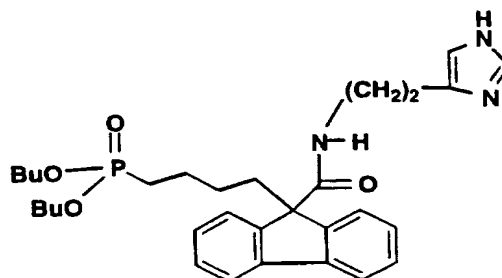
Example 179

5 MS (ES, + ions) 563 (M+H).

Example 180

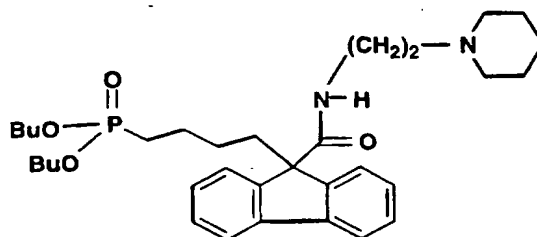
10

MS (ES, + ions) 588 (M+H).

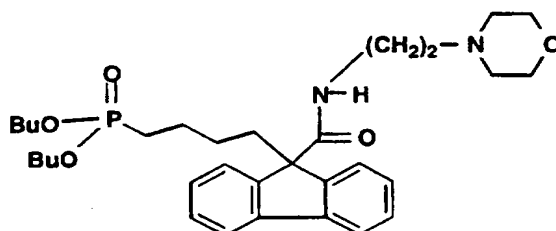
Example 181

15

MS (ES, + ions) 552 (M+H).

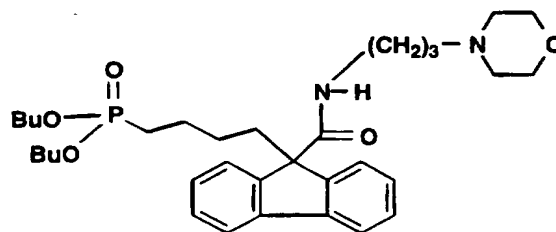
Example 182

5 MS (ES, + ions) 569 (M+H).

Example 183

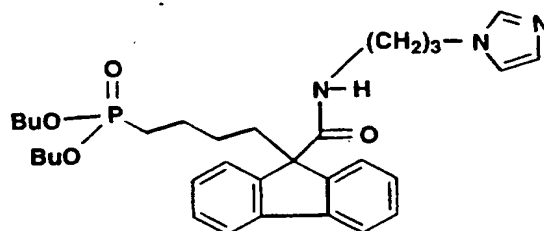
10

MS (ES, + ions) 571 (M+H).

Example 184

15

MS (ES, + ions) 585 (M+H).

Example 185

5 MS (ES, + ions) 566 (M+H).

Example 186

9-[4-(Dibutoxyphosphinyl)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

10

A solution of Example 141 Part A compound (0.90 g, 2 mmol) in 5 mL of CH₂Cl₂ was treated with oxalyl chloride in dichloromethane (1.5 mL, 3.00 mmol) and two drops of DMF. After 0.5 h, the mixture was concentrated under reduced pressure to give a yellow oil. The oil was diluted with 10 mL of tetrahydro-furan, cooled to 0°C and treated with 2,2,2-trifluoroethylamine (0.39 g, 4.00 mmol) and triethylamine (0.2 g, 2.0 mmol). The mixture was stirred for 3 h at room temperature and diluted with ethyl acetate (50 mL) and water (50 mL). The organic fraction was washed with 1N HCl (5 mL) dried over Na₂SO₄ and concentrated to a yellow oil. The oil was purified by flash column chromatography on silica gel (100 g) with 1:9 acetone/dichloromethane to give 0.69 g (59% overall yield) of title compound as a clear oil.

15 TLC Silica gel (1:9 acetone/dichloromethane) R_f = 0.3.

30 Mass Spec. (CI-NH₃, + ions) m/e 540 (M+H).

Anal. Calc'd for $C_{28}H_{37}F_3NO_4P + 0.3 H_2O$:

C, 61.76; H, 6.95; N, 2.57; F, 10.47;

P, 5.69

Found: C, 61.71; H, 6.78; N, 2.62; F, 10.66;

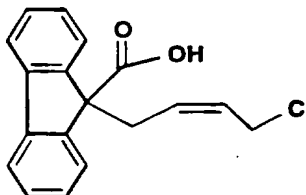
5 P, 5.47.

Alternate Example 186

9-[4-(Dibutoxyphosphinyl)butyl]-N-(2,2,2-trifluoro-
ethyl)-9H-fluorene-9-carboxamide

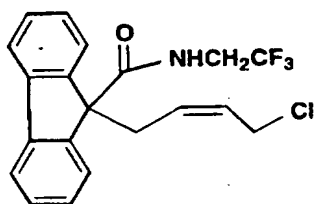
10

A.



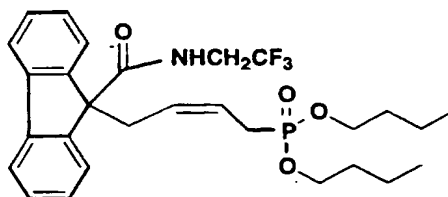
Butyllithium (8.4 mL, 2.5M in hexane, 21
15 mmol) was added dropwise over 10 min to a solution
of 9-fluorenicarboxylic acid (2.10 g, 10 mmol) in
THF (50 mL) at 0 °C under argon. During addition
of the first equivalent of BuLi, the reaction
became thick with a white precipitate which became
20 yellow and cleared after addition of the second
equivalent. The reaction was stirred at 0 °C for
20 min, then *cis*-1,4-dichloro-2-butene (1.2 mL, 11
mmol) was added dropwise over 5 min. The reaction
lightened in color during addition and was stirred
25 at 0 °C for 3 h, then poured into 1N HCl (50 mL)
and extracted with CH_2Cl_2 (3 x 50 mL). The
combined organic layers were washed with brine (30
mL) then dried over $MgSO_4$. Evaporation provided
3.5 g of a yellow oil containing crystalline solid.
30 The crude residue was triturated with hexane (20
mL). The supernatant was decanted, and the residue
pumped under high vacuum to give 2.93 g of title
compound as a tan solid.

B.



To a stirred solution of 10.0 g (33.5 mmol)
5 of Part A compound in 100 mL of dichloromethane at
RT was added 20.0 mL (40 mmol) of 2M oxalyl
chloride in dichloromethane followed by 30 μ L of
DMF. The reaction was allowed to stir at RT for 2
h when the solvent was evaporated and the semisolid
10 residue pumped (\approx 1 mm pressure) for 0.5 h. The
residue was dissolved by adding 300 mL of ether and
cooled to 0°C. The mixture was treated with 7.30 g
(67 mmol) of 2,2,2-trifluoroethylamine and warmed
to room temperature. The mixture was diluted with
15 150 mL of ethyl acetate and 100 mL of 0.5 M HCL.
The layers were separated, the organics dried
(Na₂SO₄) and concentrated. The remainder was
purified by flash column chromatography on silica
gel (250 g) eluting with 1:9 ethyl acetate/hexanes
20 (800 mL) followed by 1:5 ethyl acetate/hexanes
(1L). Pure fractions were pooled and concentrated
to give 9.25 g (73%) of title compound as a white
solid. mp: 87-89°C.

C.



A mixture of Part B compound (7.60 g, 20 mmol) and tributylphosphite (25 g, 100 mmol) was warmed to 120°C for 24 h. The volatiles were removed by short path distillation (0.2 mm Hg, 118°C) to leave 11.5 g of a colorless oil. The oil was purified by flash column chromatography on silica gel (500 g) eluting with 5:95 acetone/dichloromethane (1 L) followed by 1:5 acetone/dichloromethane (1L). Pure fractions were pooled to give 8.80 g (82%) of title compound as a colorless oil which gradually turned to a waxy solid.

TLC Silica gel (1:5 acetone/dichloromethane) R_f = 0.5.

D. 9-[4-(Dibutoxyphosphinyl)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A suspension of 8.50 g (15.8 mmol) of Part C compound in 200 mL of ethanol was warmed to 40°C for a few minutes to completely dissolve the crystalline solids. The resulting colorless solution was treated with 0.5 g of 10% Pd/carbon and the reaction vessel placed under an atmosphere of H₂ (balloon pressure). The reaction mixture was stirred for 25 h when it was filtered through a pad of celite. The colorless filtrate was filtered through a pad of celite and concentrated to give 8.3 g (95%) of title compound as a colorless oil.

The oil gradually turned to white solid on standing. mp: 71-74°C.

TLC Silica gel (1:5 acetone/dichloromethane) R_f =
5 0.5.
MS (ES, + ions) m/z 540 (M+H).

Anal. Calc'd for $C_{28}H_{37}F_3NO_4P$:
C, 62.33; H, 6.91; F, 10.56; N, 2.60; P,
10 5.74
Found: C, 62.36; H, 7.00; F, 10.63; N, 2.56; P,
5.86.

Example 187

15 9-(2-Propenyl)-9H-fluorene-9-carboxylic acid, ethyl ester

An ethanol (7 ml) solution of Example 93 Part B (275 mg, 1.04 mmol) was stirred at room
20 temperature for 1h, then stored at -20°C overnight.
After warming, the volatiles were removed in vacuo to give an oil (300 mg). The residue was purified by flash column chromatography (SiO_2 , 3 by 9 cm),
eluting with 5%EtOAc:hexanes to give title compound
25 (211 mg, 73% yield) as a colorless oil.

MS: (CI): m/z 296 (M+ NH_4)⁺.

Example 188

30 9-(4-Cyanobutyl)-N-propyl-9H-fluorene-9-carboxamide

To a solution of 400 mg (0.92 mmol) of Example 11 Part C compound in 1 mL of DMSO, under argon at RT, was added 180 mg (2.77 mmol) of
35 potassium cyanide (KCN). The mixture was stirred at RT for 18 h, at which time the reaction was diluted with ether and washed with sodium

bisulfite, NaHCO_3 , water, brine, dried (Na_2SO_4) and evaporated. Recrystallization was attained from hot hexanes to provide 225 mg (74%) of title compound as a white solid.

5

mp 102-104°C.

TLC Silica gel (95:5 dichloromethane/isopropanol)

$R_f = 0.43$.

MS (CI- NH_3 , + ions) m/e 333 (M+H).

10

Anal. Calcd. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_1$:

C, 79.48; H, 7.28; N, 8.43

Found: C, 79.17; H, 7.40; N, 8.34.

Example 189

15

1-[9-(3-Phenylpropyl)-9H-fluorene-9-yl]-1-butanone

A solution of Example 22 Part B acid chloride (4 mmol) in 15 ml of tetrahydrofuran was cooled to -20°C under an argon atmosphere and anhy.
20 copper iodide (50 mg) was added. A 2 M solution of n-propyl magnesium chloride in ether (2 ml, 4 mmol) was added over a 5 minute period. The reaction was stirred at -20°C for 2.5 hrs. and then at 0°C for 30 min. The reaction was quenched with
25 a saturated solution of ammonium chloride and extracted with ethyl acetate (3x20ml). The ethyl acetate extract was washed with water, brine and dried over anhy. sodium sulfate. The crude ketone was purified on a Merck EM silica column eluting
30 with 5% ethyl acetate/hexane yielding 850 mg (64%) of title compound as a colorless oil.

MS (CI, + ions) 355 (M+H)

Anal Calc'd for $\text{C}_{26}\text{H}_{26}\text{O}$:

35

C, 87.74; H, 7.41

Found: C, 87.70; H, 7.45.

Example 1909-(3-Phenylpropyl)- α -propyl-9H-fluorene-9-methanol

A solution of Example 189 compound (400 mg, 1.13 mmol) in 25 ml of methanol was cooled to 0°C under an argon atmosphere. Sodium borohydride (93 mg, 2.45 mmol) was added portion wise over 10 minutes and the mixture was then stirred for 30 min. longer at 0°C. The reaction was diluted with 0.1 N hydrochloric acid to pH 4. The reaction mixture was diluted with 30 ml of water and extracted with ethyl acetate (3x20 ml). The ethyl acetate extract was washed with water, brine and dried over sodium sulfate. The crude product was purified on a Merck EM silica column eluting with 10% ethyl acetate / hexane yielding 345 mg (86%) of title compound as a colorless oil.

MS (CI, + ions) 374 (M+NH₄).

Anal Calc'd for C₂₆H₂₈O+0.65 H₂O (FW 368.21):

C, 84.79; H, 8.02

Found: C, 84.83; H, 7.94.

Example 1914-Hydroxy-1-(9-propyl-9H-fluoren-9-yl)butanone

A solution of Example 59 Part B compound (1.07 g, 3.97 mmol) in THF (10 mL) under argon was cooled to 0°C. Copper (I) iodide (38 mg, 0.20 mmol) was added followed by dropwise addition of $\text{ClMg}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{OMgCl}$ (prepared analogously to Umio, et al, J. Med. Chem. 1972, 15, 855) (14.5 mL, 0.3M in THF, 4.37 mmol) over 10 min. Upon addition, a deep red color appeared but quickly dissipated with stirring. The opaque yellow reaction was stirred at 0 °C for 45 min, then quenched by addition of saturated NH₄Cl (10 mL). The reaction was diluted

with water (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with saturated NH_4Cl , water, and brine (10 mL each), then dried over MgSO_4 . Evaporation gave 1.3 g of a yellow oil, which was purified by flash chromatography on silica gel (150 g), loading in 50% EtOAc/hexane, and eluting with 25% EtOAc/hexane to provide title compound (885 mg, 76%) as a colorless oil.

Anal. Calcd. for $\text{C}_{20}\text{H}_{22}\text{O}_2 \cdot 0.5 \text{ H}_2\text{O}$:

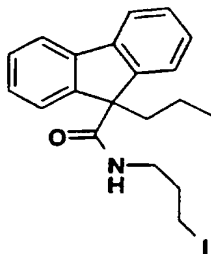
C, 79.19; H, 7.64.

Found: C, 79.07; H, 7.32.

Example 192

N-[3-(Dibutoxyphosphinyl)propyl]-9-propyl-9H-fluorene-9-carboxamide

A.



A solution of oxalyl chloride in dichloromethane (1 mL, 2.0 mmol) was added to a stirred suspension of Example 59 Part A compound (0.44 g 1.74 mmol) in 10 mL of dichloromethane. The reaction mass was treated with 1 drop of DMF, allowed to stir for 0.5 h and concentrated. The remainder was diluted with 10 mL of THF, cooled to -40° and treated with 1,3-propanolamine (0.26 g, 3.50 mmol) and warmed to RT over 3 h. The reaction mixture was diluted with 20 mL of water and 50 mL of ethyl acetate. The organic fraction was extracted with water (3X), dried (MgSO_4) and

concentrated. The crude alcohol was carried on to the next step without further characterization.

To a stirred solution of 0.50 g (1.58 mmol) of the crude alcohol, 0.46 g (1.74 mmol) of triphenyl-phosphine, and 0.21 g (3.15 mmol) of imidazole in 10 mL of THF under argon at room temperature was added a solution of 0.44 g (1.74 mmol) of iodine in 10 mL of THF, dropwise over 15 min. After the addition was complete, the reaction was stirred at RT for 2 h and diluted with 100 mL of ethyl acetate and washed with a saturated solution of Na₂SO₃. The organic phase was dried (MgSO₄) and concentrated. The residue was purified by flash chromatography on silica gel (100 g) eluted with 15:85 ethyl acetate/hexanes to give 0.42 g (64%) of title compound as a white solid.

TLC Silica gel (1:3 ethyl acetate/hexanes) R_f=0.6.
Mass Spec (CI-NH₃, + ions) m/e 420 (M+H).

20

B. N-[3-(Dibutoxyphosphinyl)propyl]-9-
propyl-9H-fluorene-9-carboxamide

A mixture of Part A compound (0.35 g, 0.83 mmol) and tributylphosphite (1.2 mL, 1.9 mmol) was warmed to 120°C for 18 h. The mixture was purified by short path distillation (0.2 mm Hg, 110°C) to leave 0.34 g of title compound as a colorless oil. The oil was purified by flash chromatography on silica gel (50 g) eluting with 1:9 isopropanol/dichloromethane to give 0.30 g (78%) of title compound as a colorless oil.

30

TLC Silica gel (5:95 2-propanol/dichloromethane)
R_f= 0.3.

35 Mass Spec. (ES, + ions) m/z 486 (M+H).

Anal. Calc'd for $C_{28}H_{40}NO_4P + 0.90 H_2O$:

C, 67.04; H, 8.39; N, 2.79

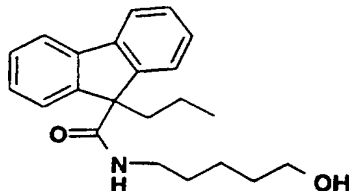
Found: C, 67.09; H, 8.54; N, 2.72.

5

Example 193

N-[5-(Dibutoxyphosphinyl)pentyl-9-propyl-9H-fluorene-9-carboxamide

A.



10

N-(5-Hydroxypentyl)-9-propyl-9H-fluorene-9-carboxamide

A solution of oxalyl chloride in dichloromethane (1 mL, 2.0 mmol) was added to a stirred suspension of Example 59 Part A compound (0.40 g 1.58 mmol) in 10 mL of dichloromethane. The reaction mass was treated with 1 drop of DMF, allowed to stir for 0.5 h and concentrated. The remainder was diluted with 10 mL of THF, cooled to -78° and treated with 1,5-pentanamine (0.41 g, 4 mmol) and warmed to RT over 3 h. The reaction mixture was diluted with 20 mL of water and 50 mL of ethyl acetate. The organic fraction was extracted with water (3X), dried ($MgSO_4$) and concentrated. The remainder was purified by column chromatography on silica gel (100 g) with 1:1 ethyl acetate/hexanes (500 mL) followed by 7:3 ethyl acetate/hexane (400 mL) to give 0.53 g (98%) of title compound as an oil. The resulting oil gradually solidified (4 days standing) to a white solid.

mp 48-51°.

TLC Silica gel (1:1 ethyl acetate/hexane) R_f = 0.3.

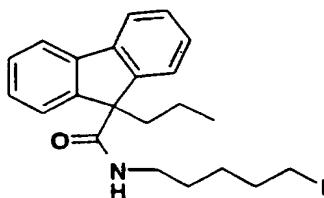
Mass Spec. (CI, + ions) m/z 338 (M+H).

Anal. Calc'd for $C_{22}H_{27}NO_2 + 0.3 H_2O$:

C, 77.13; H, 8.11; N, 4.09

5 Found: C, 77.10; H, 8.23; N, 4.00.

B.



- 10 To a stirred solution of 0.50 g (1.50 mmol)
of Part A compound, 0.47 g (1.80 mmol) of
triphenyl-phosphine, and 0.20 g (3.00 mmol) of
imidazole in 10 mL of THF under argon at room
temperature was added a solution of 0.46 g (1.8
15 mmol) of iodine in 10 mL of THF, dropwise over 15
min. After the addition was complete, the reaction
was stirred at RT for 2 h and diluted with 100 mL
of ethyl acetate and washed with a saturated
solution of Na_2SO_3 . The organic phase was dried
20 ($MgSO_4$) and concentrated. The residue was purified
by flash chromatography on silica gel (100 g)
eluted with 15:85 ethyl acetate/hexanes to give
0.58 g (87%) of title compound as a colorless oil.
- 25 TLC Silica gel (1:9 ethyl acetate/hexanes) $R_f=0.3$.
Mass Spec (CI-NH₃, + ions) m/e 448 (M+H).

C. N-[5-(Dibutoxyphosphinyl)pentyl]-9-propyl-9H-fluorene-9-carboxamide

- 30 A mixture of Part B compound (0.28 g, 0.63
mmol) and tributylphosphite (2 mL, 8 mmol) was
warmed to 120°C for 18 h. The volatiles were
removed by short path distillation (0.2 mm Hg,

110°C) to leave 0.30 g (88%) of title compound as a colorless oil.

TLC Silica gel (5:95 2-propanol/dichloromethane)

5 R_f = 0.3.

Mass Spec. (ES, + ions) m/z 536 (M+Na), 514 (M+H).

Anal. Calc'd for C₃₀H₄₄NO₄P + 1.0 H₂O:

C, 67.62; H, 8.73; N, 2.63; P, 5.81

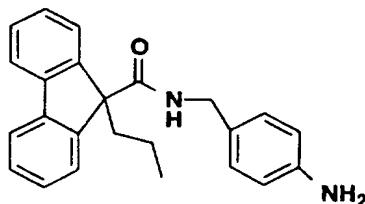
10 Found: C, 67.31; H, 8.33; N, 2.94; P, 6.05.

Example 194

N-[[4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)phenyl]-
methyl]-9-propyl-9H-fluorene-9-carboxamide

15

A.

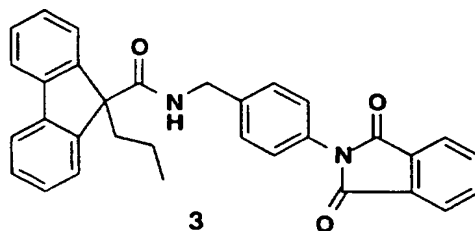


To a stirred solution of Example 59 Part A compound (1.0 g, 3.91 mmol) and triethylamine (0.6 mL, 4.30 mmol) in THF (10 mL) at -20°C was added dropwise isobutyl chloroformate (0.56 mL, 4.30 mmol). After stirring at -20°C for 30 min, the reaction containing a white precipitate was filtered through a fritted funnel to obtain a clear solution. To a stirred solution of 4-aminobenzylamine (0.49 mL, 4.30 mmol) in THF (10 mL) at -20°C was added dropwise the mixed anhydride solution over 30 min. The reaction was stirred at -20°C for 3 hrs, then warmed to RT. Dichloromethane (300 mL) was added to dilute the reaction. The resulting solution was washed with H₂O (2 x 50 mL), saturated sodium bicarbonate solution (2 x 50 mL), brine (2 x 50 mL) and dried over MgSO₄. The volatiles were removed under reduced

pressure to afford title compound (1.2 g, 85%) as a solid. (mp 96-99°C, recrystallized from isopropanol/hexane).

5

B.



A mixture of Part A compound (500 mg, 1.39 mmol) and phthalic anhydride (206 mg, 1.39 mmol) was heated at 150°C for 30 min then cooled to RT. The reaction was triturated with methanol (5 mL), and the solid filtered and dried under vacuum to give title compound (440 mg, 65%) as a yellow solid.

15

C. N-[[4-(1,3-Dihydro-1-oxo-2H-isoin-2-yl)phenyl]methyl]-9-propyl-9H-fluorene-9-carboxamide

To stirred solution of Part B compound (420 mg, 0.86 mmol) in THF/MeOH (1:1, 8 mL) at 0°C was added sodium borohydride (33 mg, 0.86 mmol). The reaction was stirred at 0 °C for 30 min then warmed to RT. Stirring was continued for 2 h. The reaction was quenched with acetic acid until the reaction pH = 5. Dichloromethane (150 mL) was added to dilute the reaction and the solution was washed with saturated sodium bicarbonate (2 x 30 mL), H₂O (2 x 30 mL), brine (2 x 30 mL) and dried over MgSO₄. Evaporation gave a yellow solid. The residue was dissolved in trifluoroacetic acid (4 mL) at RT. Triethylsilane (0.42 mL, 2.58 mmol) was added. The reaction was stirred at RT for 30 min then evaporated to dryness. The residue was

trituated with methanol (2 mL), filtered and dried to give title compound (260 mg, 64%) as a white powder.

5 mp 238-240°C.

Anal. Calc. for $C_{32}H_{28}N_2O_2 \cdot 0.4H_2O$:

C, 80.11; H, 6.05; N, 5.84

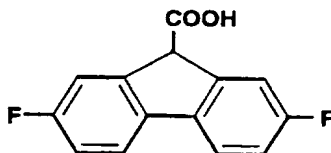
Found: C, 79.96; H, 5.84; N, 5.85.

10

Example 195

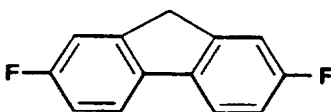
(E)-9-[4-(Dibutoxyphosphinyl)-2-butenyl]-2,7-difluoro-N-propyl-9H-fluorene-9-carboxamide

A.



15

A(1).



20

To a THF (25 ml) suspension of 2,7-diamino-fluorene (7.17 g, 0.036 mol) at -10°C under argon was added aqueous HBF_4 (71 mL, 1.13 mol, 48-50%). Near the end of addition stirring became difficult due to solid formation, although most of the solid went into solution upon complete addition of acid. A saturated aqueous solution of sodium nitrite (7.1 g in 11 mL, 0.103 mol) was added and after 1.5 h the mixture was filtered, washing with 5% aq. HBF_4 , MeOH, then ether, and the collected solid dried briefly on the filter flask. The resulting brown solid (9.7 g) was used in the subsequent reaction.

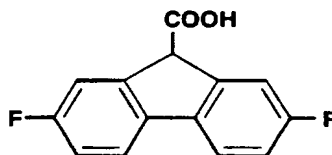
25

30

The above solid was suspended in xylenes (100 ml) and heated to 110°C for 2 h, with gas evolution observed, then brought to reflux for an

additional 2 h. The solution was decanted from a black tar in the reaction flask and the volatiles removed under high vacuum to give a dark tan solid (7.5 g). The solid was crystallized from hot EtOH to give title compound (1.4 g) as a colorless solid. An ether wash of the black tar was combined with the mother liquor and concentrated *in vacuo*. The oily-solid residue (4.3 g) was purified by flash column chromatography (SiO₂, 9 by 16 cm), eluting with hexanes then 2.5% EtOAc:hexanes, to give title compound (2.44 g, total 3.84 g, 52% yield) as a colorless solid.

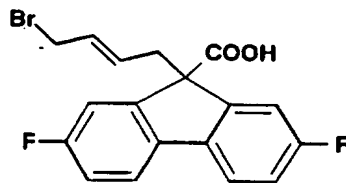
A(2).



15

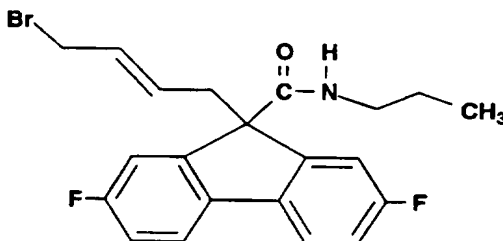
To a THF (15 ml) solution of Part A(1) compound (1.38 g, 6.82 mmol) at -5°C (ice/brine bath) under argon was added dropwise n-BuLi (3.4 ml, 8.50 mmol, 2.5 M in hexanes). After 1.15 h, crushed solid CO₂ (excess) was added, followed by Et₂O (~5 ml), and the reaction allowed to stir at room temperature for 19 h. The brown colored reaction mixture was cooled to 0°C, quenched with 2N HCl, and the aqueous layer extracted twice with EtOAc. The combined organics were dried over Na₂SO₄ and evaporated *in vacuo* to give crude title compound (1.64 g, 98% recovery, contaminated with A(1), seen by ¹H NMR), as a colorless solid suitable for the next reaction. Trituration with hexanes can remove unreacted starting material Compound A(1).

B.



A solution of Part A 2,7-difluorofluorene-9-carboxylic acid (500mg, 2.05 mmol) in 5 ml of THF was cooled to -30°C under an argon atmosphere and 2 equiv. of a 2.5 M solution of n-butyl lithium in hexane (1.64 ml, 4.1 mmol) was added. The mixture was stirred for 5 min. at -30°C and was then added to a cold (-30°C) solution of 1,4-dibromo-2-butene (2.14 g, 10 mmol) in 4 ml of THF. The reaction mixture was stirred at -30°C for 30 min and was then quenched with 1 N HCl and extracted with ethyl acetate (3x10 ml). The ethyl acetate extract was washed with water, brine and dried over anhy. sodium sulfate. The crude title material was purified on a Merck EM silica column eluting with 5% isopropanol/dichloro-methane yielding 480 mg (62%) as a colorless solid, m.p. 142-146°C. (Mass Spec. M+H = 380).

C.



The Part B carboxylic acid (476 mg, 1 mmol) was dissolved in 12 ml of dichloromethane and DMF (50 µl) was added. The mixture was cooled to 0°C under an argon atmosphere and oxalyl chloride (178 mg, 1.4 mmol) was added and the mixture allowed to warm to ambient temperature and stir for 2.5 hrs.

The mixture was evaporated several times from dichloromethane yielding the crude acid chloride as a pale yellow solid.

5 The acid chloride was dissolved in 8 ml of THF and cooled to 0°C under an argon atmosphere. Triethylamine (152 mg, 1.5 mmol) was added followed by the addition of n-propyl amine (77 mg, 1.3 mmol). The reaction was allowed to warm to ambient temperature and stir overnight. The reaction was
10 quenched by adding sat. sodium bicarbonate and extracted with dichloromethane (4x20 ml). The crude product was purified on a Merck EM silica column eluting with 5% ethyl acetate/hexane yielding 420 mg (80%) of title compound as a pale
15 yellow oil, (Mass Spec, M+H = 421).

D. (E)-9-[4-(Dibutoxyphosphinyl)-2-butenyl]-2,7-difluoro-N-propyl-9H-fluorene-
9-carboxamide

20 A solution of Part C compound (400 mg, 0.95 mmol) in tributyl phosphite (1.8 ml) was heated at 90°C overnight. Excess tributyl phosphite was removed under vacuum at 100°C and the oily residue was purified on a Merck EM silica column eluting
25 with 3% isopropanol / dichloromethane yielding 353 mg (70%) of title compound as a colorless oil.

MS (CI, + ions) 534 (M+H).

Anal Calc'd for $C_{29}H_{38}NF_2PO_4 + 0.3 H_2O$:

30 C, 64.61; H, 7.22; N, 2.60

Found: C, 64.69; H, 7.50; N, 2.52.

Example 196

9-[4-(Dibutoxyphosphinyl)butyl]-2,7-difluoro-N-propyl-9H-fluorene-9-carboxamide

5 An ethanol solution of Example 195 compound (260 mg, 0.49 mmol) containing 50 mg of 10% palladium on carbon was stirred under a hydrogen atmosphere (balloon) for 14 hrs. The reaction was filtered through a 0.2 μ m nylon filter to remove
10 the catalyst and the solvent evaporated yielding 235 mg (90%) of title compound as a colorless oil.

MS (CI, + ions) 536 (M+H).

Anal Calc'd for $C_{29}H_{40}NF_2PO_4 + 0.5 H_2O$:

15 C, 64.73; H, 7.54; N, 2.60

Found: C, 64.78; H, 7.50; N, 2.55.

Example 197

9-[4-(Diethoxyphosphinyl)butyl]-N-propyl-9H-fluorene-9-carboxamide

To 400 mg (0.92 mmol) of Example 11 Part C compound was added 475 μ L (2.77 mmol) of triethylphosphite (neat). The mixture was heated to 120°C
25 for 18 h and bulb to bulb distilled (5 mm, 100°C) to remove lower boiling impurities and provide a yellow oil. Flash chromatography was performed on 50 g of silica gel eluting with 97:3 dichloromethane/isopropanol to provide 300 mg
30 (75%) of title compound as a pale yellow oil.

TLC Silica gel (95:5 dichloromethane/isopropanol)
 R_f = 0.38.

MS (CI-NH₃, + ions) m/e 444 (M+H).

35

Anal. Calcd. for $C_{25}H_{34}NO_4P + 0.75 \text{ mol } H_2O$:

C, 65.20; H, 7.85; N, 3.04; P, 6.73

Found: C, 65.30; H, 7.57; N, 2.94; P, 6.53.

5

Example 198

9-[4-(Diphenylphosphinyl)butyl]-N-propyl-9H-
fluorene-9-carboxamide

To 400 mg (0.92 mmol) of Example 11 Part C
10 compound was added 600 μL (2.77 mmol) of
ethyldiphenyl phosphinite (neat, Aldrich). The
mixture was heated to 120°C for 18 h. Flash
chromatography was performed on 100 g of silica gel
eluting with 97:3 dichloromethane/isopropanol to
15 provide a white solid, which was further purified
by crystalization from hot methanol triturated with
water to provide 100 mg (22%) of title compound as
a white solid. mp $163\text{--}165^\circ\text{C}$.

20 TLC Silica gel (95:5 dichloromethane/isopropanol)
 $R_f = 0.34$.
MS (CI- NH_3 , + ions) m/e 508 (M+H).

Anal. Calcd. for $C_{33}H_{34}NO_2P$:

25 C, 78.08; H, 6.75; N, 2.76; P, 6.10

Found: C, 77.75; H, 6.76; N, 2.73; P, 5.97.

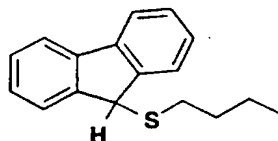
^{13}C NMR (75 MHz, CDCl_3) is consistent with the
indicated compound.

30

Example 199

[4-[9-(Butylthio)-9H-fluoren-9-yl]butyl]phosphonic acid, dibutyl ester

A.



A solution of 9-acetoxy-(9H)-fluorene (1.00 g, 4.46 mmol) and butanethiol (0.34 g, 3.79 mmol) in 10 mL of dichloromethane at -20°C was treated with borontri-flouride etherate (0.59 g, 4.17 mmol). The reaction was stirred for 1 h at -20°C and warmed to room temperature. After stirring for 18 h the contents of the flask were purified by column chromatography on silica gel (100 g) with hexanes followed by 1:9 dichloromethane/hexanes to give 0.76 g (98%) of title compound as a colorless oil.

TLC Silica gel (1:9 dichloromethane/hexanes) R_f= 0.5.

¹³C NMR (CDCl₃, 75 MHz) δ 145.1, 140.6, 127.8, 127.4, 125.4, 119.7, 48.8, 31.1, 27.4, 21.8, 13.5 ppm.

B. [4-[9-(Butylthio)-9H-fluoren-9-yl]butyl]-phosphonic acid, dibutyl ester

A solution of Part A compound (0.76 g, 2.99 mmol) in 10 mL of THF at -78°C was treated with n-butyllithium in hexanes (1.64 mL, 4.09 mmol) followed by Example 11 Part B bromide (1.15 g, 3.50 mmol). The reaction was stirred for 0.5 h and warmed to room temperature for 18 h. The contents of the flask were diluted with 30 mL of aqueous NH₄Cl solution and 30 mL of ethyl acetate. The

organic fraction was dried (Na_2SO_4) and concentrated. The remainder was purified by column chromatography on silica gel (50 g) with 2:98 acetone/dichloromethane (500 mL) followed by 5:95 acetone/dichloromethane to give 0.90 (66%) of title compound as a colorless oil.

TLC Silica gel (5:95 acetone/dichloromethane)
 $R_f = 0.6$.

Mass Spec. (ES, + ions) m/e 520 ($M+\text{NH}_4$), 503 ($M+H$).

Anal. Calc'd for $\text{C}_{29}\text{H}_{43}\text{O}_3\text{PS} + 1.35 \text{ H}_2\text{O}$:

C, 66.10; H, 8.74; P, 5.88; S, 6.08

Found: C, 65.72; H, 8.29; P, 5.99; S, 5.71.

Example 200

[4-[9-(Butylsulfonyl)-9H-fluoren-9-yl]butyl]phosphinic acid, dibutyl ester

To a suspension of Example 199 Part B compound (0.35 g, 0.69 mmol) in dichloromethane (5 mL) at 0°C was added 3-chloroperoxybenzoic acid (m-CPBA) (0.52 g, 50% by weight ≈ 0.152 mmol) in one portion. The mixture was stirred for 1 h when it was diluted with 0.1 M KOH (20 mL) and ether (30 mL). The organic fraction was dried (Na_2SO_4) and concentrated. The remainder was purified by column chromatography on silica gel (50 g) with 1:9 acetone/dichloromethane to give 0.32 g (86%) of title compound as a colorless oil.

TLC Silica gel (1:9 acetone/dichloromethane) $R_f = 0.5$.

Mass Spec. (CI- NH_3 , + ions) m/e 535 ($M+H$), 413 ($M+H-\text{C}_4\text{H}_9\text{SO}_2$).

Anal. Calc'd for $C_{29}H_{43}O_5SP + 0.3 H_2O$:

C, 64.40; H, 8.14; P, 5.73; S, 5.93

Found: C, 64.38; H, 7.94; P, 5.63; S, 5.52.

5

Example 201

[4-[9-(Butylsulfinyl)-9H-fluoren-9-yl]butyl]phosphonic acid, dibutyl ester

To a suspension of Example 199 Part B
10 sulfide (0.40 g, 0.80 mmol) in dichloromethane (5 mL) at 0°C was added 3-chloroperoxybenzoic acid (0.34 g, 50% by weight \approx 0.80 mmol) in one portion. The mixture was stirred for 1 h when it was diluted with 0.1 M KOH (10 mL) and ether (30 mL). The
15 organic fraction was dried (Na_2SO_4) and concentrated. The remainder was purified by column chromatography on silica gel (50 g) with 2:8 acetone/dichloromethane to give 0.25 g (60%) of title compound as a colorless oil.

20

TLC Silica gel (1:4 acetone/dichloromethane) R_f = 0.3.

Mass Spec. (ES, + ions) m/e 1054 (2M+H), 519 (M+H).

25 Anal. Calc'd for $C_{29}H_{43}O_4SP + 0.85 H_2O$:

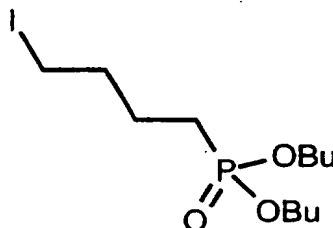
C, 65.23; H, 8.44; P, 5.80; S, 6.00

Found: C, 65.23; H, 8.30; P, 5.99; S, 5.71.

Example 2025-[4-(Dibutoxyphosphinyl)butyl]-N-propyl-5H-indeno-[1,2-b]pyridine-5-carboxamide

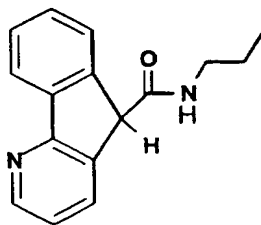
5

A.



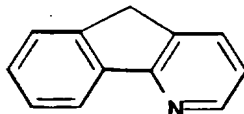
To a THF (10 ml) solution of dibutyl phosphite (4 g, 0.021 mol) at 0°C under argon was added dropwise sodium hexamethyldisilazane (21 ml, 1 M in THF), with the reaction mixture turning a yellow color. After 20 min, 1,4-diiodobutane (6.58 g, 0.021 mol) was added and the reaction kept at 0°C for 1.15 h, and 5°C overnight. The reaction was quenched with sat. NH₄Cl and the aqueous layer was extracted with EtOAc. The organics were dried over Na₂SO₄ and concentrated to an oil (8 g). The residue was purified by flash column chromatography (SiO₂, 5 by 15 cm), eluting with CH₂Cl₂, then 10% EtOAc:CH₂Cl₂, to give title compound (1.9 g, 24% yield) as a colorless oil. MS: (CI, M+H⁺): m/z 377.

B.



25

B(1).

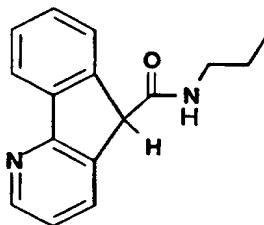


- A suspension of 4-aza-9-fluorenone (4 g, 0.022 mol) in hydrazine hydrate (4 ml) and diethylene glycol (40 ml) under argon was heated to 105-110°C for 1 h, then the resulting orange colored suspension was heated to 200°C for 1.5 h. The reaction was cooled and then poured into H₂O.
- The aqueous layer was extracted twice with EtOAc, the combined organics washed with brine, dried over Na₂SO₄, and concentrated to a colorless solid (3.8 g). The residue was crystallized from hot hexanes, with seeding, to give title compound (2.91 g, 76% yield, contaminated with 4% diethylene glycol) as a colorless solid. mp 91-93°C MS: (CI, M+H⁺): m/z 168.

Anal. Calc. for C₁₂H₉NO • 0.07 H₂O:

- C, 85.56; H, 5.47; N, 8.31
Found: C, 85.56; H, 5.39; N, 8.31.

B(2).



- To a THF (7 ml) solution of Part B(1) compound (405 mg, 2.42 mmol) and propyl isocyanate (227 mg, 2.67 mmol) at -10°C under argon was added dropwise sodium hexamethyldisilazane (3 ml, 1 M in THF), with the reaction mixture turning a red color. After 15 min and 35 min, more propyl isocyanate (200 then 136 mg, 3.95 mmol) was added.

The reaction solution turned to a green color upon the third addition of isocyanate and the reaction was quenched with sat. NH_4Cl . The aqueous layer was extracted twice with EtOAc, the combined
5 organics dried over Na_2SO_4 , and concentrated to an oily-solid (1 g). The residue was combined with a similar reaction (from 0.55 mmol of Part B(1) compound) and was purified by flash column chromatography (SiO_2 , 5 by 9.5 cm), eluting with
10 30, 35, 40, then 50% EtOAc: CH_2Cl_2 , to give title compound (287 mg, 39% yield) as a colorless solid. mp 171-172°C; MS: (electrospray, $\text{M}+\text{H}^+$): m/z 253.

15 C. 5-[4-(Dibutoxyphosphinyl)butyl]-N-propyl-5H-indeno[1,2-b]pyridine-5-
carboxamide

To a THF (3 ml, degassed) suspension of Part B compound (200 mg, 0.793 mmol), at 0°C under argon was added dropwise n-BuLi (0.7 ml, 2.5 M in
20 hexanes), with a red colored solid falling from solution after all the base was added. After 10 min, Part A compound (325 mg, 0.864 mmol) was added and the reaction stirred an additional 2 h. The brown reaction mixture was quenched with sat. NH_4Cl
25 and the aqueous layer was extracted twice with EtOAc, the combined organics dried over Na_2SO_4 , and concentrated to a brown colored oil (400 mg). The residue was purified by flash column chromatography (SiO_2 , 5 by 9.5 cm), eluting with 27 and 35%
30 $\text{CH}_3\text{CN}:\text{CH}_2\text{Cl}_2$, then 4 and 10% iPrOH: CH_2Cl_2 , to give title compound (184.5 mg, 46% yield) as a colorless solid. mp 93.5-96°C.

MS: (CI, $\text{M}+\text{H}^+$): m/z 501.

35

Anal. Calc. for $C_{26}H_{41}N_2O_4P$:

C, 67.18; H, 8.25; N, 5.60; P 6.19

Found: C, 67.24; H, 8.28; N, 5.61; P 5.83.

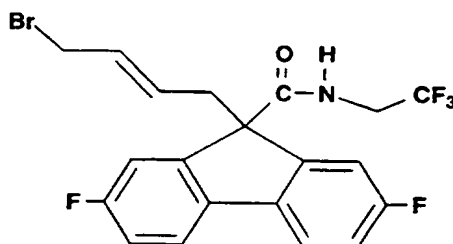
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Example 203

(E)-9-[4-(Dibutoxyphosphinyl)-2-butenyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

10

A.



The Example 195 Part B carboxylic acid (465 mg, 1.23 mmol) was dissolved in 10 ml of dichloromethane and DMF (50 μ l) was added. The mixture was cooled to 0°C under an argon atmosphere and oxalyl chloride (165 mg, 1.3 mmol) was added and the mixture allowed to warm to ambient temperature and stir for 2.5 hrs. The mixture was evaporated several times from dichloromethane yielding the crude acid chloride as a pale yellow solid.

The acid chloride was dissolved in 5 ml of THF and cooled to 0°C under an argon atmosphere. Triethylamine (142 mg, 1.4 mmol) was added followed by the addition of 2,2,2-trifluoroethylamine (139 mg, 1.4 mmol). The reaction was allowed to warm to ambient temperature and stir overnight. The reaction was quenched by adding sat. sodium bicarbonate and extracted with ethyl acetate (3x20 ml). The crude product was purified on a Merck EM silica column eluting with 10% ethyl acetate / hexane yielding 230 mg (38%) of title compound as a pale yellow solid, (Mass Spec, M+H = 461).

B. (E)-9-[4-(Dibutoxyphosphinyl)-2-butenyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

5 A solution of Part A compound (230 mg, 0.5 mmol) in tributyl phosphite (3 ml) was heated at 110°C overnight. Excess tributyl phosphite was removed under vacuum at 100°C and the oily residue was purified on a Merck EM silica column eluting
10 with 3% isopropanol/dichloromethane yielding 186 mg (68%) of title compound as a colorless solid, m.p. 142-144°C.

MS (CI, + ions) 574 (M+H).

15 Anal Calc'd for $C_{28}H_{33}NF_5PO_4 + 0.3 H_2O$:

C, 58.63; H, 5.80; N, 2.44; F, 16.56; P, 5.40

Found: C, 58.91; H, 5.88; N, 2.47; F, 16.24; P, 5.50.

20

Example 204

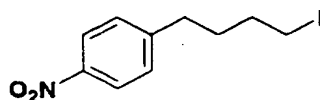
9-[4-[4-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-phenyl]butyl]-N-propyl-9H-fluorene-9-carboxamide

25 A. 9-[4-(4-Aminophenyl)butyl]-N-propyl-9H-fluorene-9-carboxamide

A(1). 9-[4-(4-Nitrophenyl)butyl]-N-propyl-9H-fluorene-9-carboxamide

30

A(1)a.



A solution of iodine (1.40 g, 5.5 mmol) in
35 THF (5 mL) was added dropwise over 5 min to a solution of 4-(4-nitrophenyl)-1-butanol (975 mg, 5

mmol), triphenylphosphine (1.44 g, 5.5 mmol), and imidazole (749 mg, 11 mmol) in THF (10 mL) under argon at RT. The dark orange solution was stirred at RT for 15 min, diluted with hexane (50 mL), then
5 washed with 10% sodium bisulfite, saturated NaHCO₃, and brine (20 mL each). The organic layer was dried over MgSO₄ and filtered. To the filtrate was added silica gel (4 g) and the mixture was concentrated in vacuo to give a yellow powder,
10 which was purified by flash chromatography on silica gel (120 g) eluting with 25% CH₂Cl₂/hexane to give title compound (1.33 g, 87%) as a pale yellow crystalline solid (mp 44-45°C).

15 A(1)b. 9-[4-(4-Nitrophenyl)butyl]-N-
 propyl-9H-fluorene-9-carboxamide

 Butyllithium (1.8 mL, 2.5M in hexane, 4.4 mmol) was added to a solution of 9-fluorene-carboxylic acid (purchased from Aldrich Chemical
20 Co.) (420 mg, 2.0 mmol) in THF (10 mL) at 0°C under argon over 5 min. The reaction went from a clear solution to a white suspension then to a yellow solution during addition. The reaction was stirred at 0°C for 20 min, whereupon a solution of Part
25 A(1)a iodide (671 mg, 2.2 mmol) in THF (4 mL) was added dropwise over 5 min. The reaction was stirred at 0°C for 1.5 h, warmed to RT, then stirred at RT for 3.5 h. The reaction was quenched with 1N HCl to pH <2, diluted with water (10 mL),
30 then extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water and brine (10 mL each), then dried over MgSO₄. Evaporation gave a residue, which was azeotroped with toluene (10 mL) to give 870 mg of a dark foam.
35 To a solution of the crude acid prepared above containing 3 drops of DMF in CH₂Cl₂ (6 mL) at RT under argon was added oxalyl chloride (1.5 mL,

2.0M in CH₂Cl₂, 3.0 mmol). The reaction bubbled for 10 min, then was allowed to stir at RT for 1.5 h. The reaction was concentrated in vacuo to provide a dark oil, which was diluted with CH₂Cl₂ (5 mL) and cooled to 0°C under argon. Propylamine (493 µL, 6.0 mmol) was added dropwise over 2 min, and the reaction was stirred at 0°C for 15 min. The reaction was partitioned between EtOAc (30 mL) and water (10 mL). The organic layer was washed with 1N HCl (2 x 5 mL) and brine (5 mL), then dried over MgSO₄. Evaporation gave 974 mg of a brown oil, which was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography on silica gel (75 g) eluting with 20% EtOAc/hexane to afford title compound (705 mg, 82%) as a waxy, yellow solid.

mp 109-110°C.

Anal. Calcd. for C₂₇H₂₈N₂O₃:

C, 75.68; H, 6.59; N, 6.54

Found: C, 75.70; H, 6.58; N, 6.57.

A(2). 9-[4-(4-Aminophenyl)butyl]-N-propyl-9H-fluorene-9-carboxamide

A mixture of Part A(1) compound (628 mg, 1.47 mmol) and 10% palladium on carbon (74 mg, 0.07 mmol) in EtOAc (5 mL) was hydrogenated (balloon) at RT for 5 h, filtered through Celite with the aid of EtOAc, then concentrated in vacuo to give a residue, which was pumped under high vacuum to provide title compound (588 mg, 100%) as a yellow gum.

MS (CI, + ions) m/z 399 (M+H).

Anal. Calcd. for $C_{27}H_{30}N_2O \cdot 0.3 H_2O$:

C, 80.28; H, 7.64; N, 6.93

Found: C, 80.37; H, 7.53; N, 7.34.

- 5 B. 9-[4-[4-(1,3-Dihydro-1,3-dioxo-2H-
isoindol-2-yl)phenyl]butyl]-N-propyl-9H-
fluorene-9-carboxamide

A mixture of Part A compound (342 mg, 0.859 mmol) and phthalic anhydride (127 mg, 0.859 mmol) was heated neat at 140 °C. The reaction bubbled (water evolution) for 10 min, then the reaction was allowed to stir for an additional 15 min. The reaction was cooled to RT, and the resulting glassy solid was dissolved in a minimum amount of CH_2Cl_2 and purified by flash chromatography on silica gel (50 g) eluting with 35% EtOAc/hexane to provide title compound (380 mg, 84%) as a yellow oil.

MS (CI, + ions) m/z 529 (M+H).

Anal. Calcd. for $C_{35}H_{32}N_2O_3 \cdot 0.2 CH_2Cl_2$:

C, 77.48; H, 5.99; N, 5.13.

Found: C, 77.18; H, 6.20; N, 4.87.

25 Example 205

9-[4-[4-[(2-Phenoxyphenyl)carbonyl]amino]phenyl]-
butyl]-N-propyl-9H-fluorene-9-carboxamide

To a solution of 2-phenoxybenzoic acid (Aldrich Chemical Co.) (111 mg, 0.518 mmol) and DMF (2 drops) in CH_2Cl_2 (1.5 mL) was added oxalyl chloride (389 μ L, 2.0M in CH_2Cl_2 , 0.777 mmol). The reaction bubbled for 10 min, then was stirred at RT under argon for 1.5 h. The reaction was concentrated in vacuo, and the resulting residue was dissolved in CH_2Cl_2 (1.5 mL) and added dropwise to a solution of Example 204 Part A compound (172

mg, 0.432 mmol) and triethylamine (90 μ L, 0.648 mmol) in CH_2Cl_2 (1.5 mL) at 0°C under argon. The reaction was stirred at 0°C for 10 min, diluted with CH_2Cl_2 (20 mL), washed with saturated NaHCO_3 (5 mL) and brine (5 mL), then dried over Na_2SO_4 . Evaporation gave a yellow oil, which was dissolved in a minimum amount of CH_2Cl_2 and purified by flash chromatography on silica gel (50 g) eluting with 30% EtOAc/hexane to provide title compound (211 mg, 82%) as a yellow gum.

MS (CI, + ions) m/z 595 (M+H).

Anal. Calcd. for $\text{C}_{40}\text{H}_{38}\text{N}_2\text{O}_3 \cdot 0.4 \text{ CH}_2\text{Cl}_2$:
C, 77.18; H, 6.22; N, 4.46
Found: C, 77.18; H, 6.20; N, 4.87.

Example 206

9-[4-[4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-phenyl]-butyl]-N-propyl-9H-fluorene-9-carboxamide

Sodium borohydride (22 mg, 0.574 mmol) was added to a solution of Example 204 compound (303 mg, 0.574 mmol) in THF/EtOH (3:7, 5 mL) at 0°C under argon. The reaction was stirred at 0°C for 30 min, then allowed to warm to RT overnight. The reaction was adjusted to slightly acidic pH with glacial acetic acid (few drops), then concentrated in vacuo. The resulting residue was partitioned between CH_2Cl_2 (20 mL) and saturated NaHCO_3 (5 mL). The organic layer was washed with brine (5 mL) then dried over Na_2SO_4 . Evaporation gave 285 mg of a yellow foam.

To the hydroxylactam prepared above was added triethylsilane (137 μ L, 0.861 mmol) followed by trifluoroacetic acid (2 mL). The reaction was stirred at RT under argon for 20 min, then

concentrated in vacuo. The resulting orange oil was purified by flash chromatography on silica gel (50 g) eluting with 4% EtOAc/CH₂Cl₂ to afford title compound (243 mg, 82%) as a white solid.

5

mp 147-148.5°C.

MS (CI, + ions) m/z 515 (M+H).

Anal. Calcd. for C₃₅H₃₄N₂O₂:

10

C, 81.68; H, 6.66; N, 5.44

Found: C, 81.54; H, 6.65; N, 5.45.

Example 207

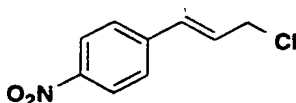
9-[3-[4-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-
15 phenyl]propyl]-N-propyl-9H-fluorene-9-carboxamide

A. 9-[3-(4-Aminophenyl)propyl]-N-propyl-
9H-fluorene-9-carboxamide

20

A(1). 9-[3-(4-Nitrophenyl)-2-propenyl]-N-
propyl-9H-fluorene-9-carboxamide

A(1)a.

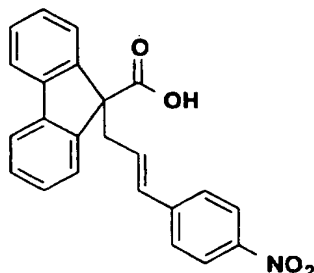


25

To a solution of N-chlorosuccinimide (2.23 g, 16.7 mmol) in dichloromethane (40 mL) at -40°C was added dropwise methyl sulfide (1.64 mL, 22.3 mmol). The reaction was stirred at -40°C for 30
30 min, then warmed to RT for 60 min. The reaction was recooled to -40°C, and a solution of 4-nitrocinnamyl alcohol (2.50 g, 13.9 mmol) in dichloromethane (4 mL) was added dropwise. The
35 reaction was stirred at -40°C for 2 h then warmed to RT overnight. Ethyl acetate (200 mL) was added to dilute the reaction and the solution was washed

with water (2 x 50 mL), brine (2 x 50 mL) and dried over MgSO₄. Evaporation gave title compound (2.50 g, 91%) as a crude oil.

5 A(1)b.



9-[3-(4-Nitrophenyl)-2-propenyl]-9-fluorene-9-carboxylic acid

10 To a solution of 9-fluorene-9-carboxylic acid (1.0 g, 4.76 mmol) in THF (20 mL) at 0°C was added dropwise a solution of n-butyllithium (2.5M, 4.2 mL, 10.5 mmol) in THF. The dark reaction was stirred at 0°C for 20 min, then a solution of Part
15 A(1)a chloride (1.04 g, 5.24 mmol) in THF (2 mL) was added dropwise over 5 min. The reaction was stirred at 0°C for 4.5 h and the dark color faded away gradually. Hydrochloric acid (1.0M, 2 mL) was added to quench the reaction. Ethyl acetate (200
20 mL) was added and the organic layer was washed with water (2 x 50 mL), brine (2 x 50 mL) and dried over MgSO₄. Evaporation gave title compound (1.7 g, 87%) as a yellowish oil.

25 A(1)c. 9-[3-(4-Nitrophenyl)-2-propenyl]-N-propyl-9H-fluorene-9-carboxamide

To a solution of Part A(1)b compound (1.65 g, 4.45 mmol) and DMF (1 drop) in dichloromethane (15 mL) at RT was added dropwise a solution of
30 oxalyl chloride in dichloromethane (2.0M, 3.34 mL, 6.67 mmol). Bubbling of escaping gasses continued for 10 min after addition. The reaction was

stirred at RT for 60 min, then concentrated in vacuum to give a dark oil. The crude acid chloride was dissolved in dichloromethane (10 mL) and cooled to 0°C under argon. Propylamine (1.1 mL, 13.4 mmol) was added dropwise over 3 min. The reaction was stirred at 0°C for 30 min. Ethyl acetate (100 mL) was added to dilute the reaction and the resulting solution was washed with H₂O (2 x 30 mL), HCl (1.0M, 2 x 30 mL), saturated sodium carbonate solution (2 x 30 mL), brine (2 x 30 mL) and dried over MgSO₄. Evaporation gave a crude gum. Purification was performed by flash chromatography on silica gel (100 g), loaded and eluted with 20% ethyl acetate in hexane. Pure fractions were combined and evaporated to give a yellow solid (1.10 g, 60%). A portion of the resulting product (300 mg) was recrystallized from ethyl acetate/hexane to give title compound (200 mg, 67%) as a yellow solid.

20

m.p. 143-146°C.

MS (CI, + ions) m/z 413 (M+H).

Anal. Calc. for C₂₆H₂₄N₂O₃ • 0.3H₂O:

25 C, 74.73; H, 5.93; N, 6.70

Found: C, 74.54; H, 5.75; N, 6.67.

A(2). 9-[3-(4-Aminophenyl)propyl]-N-
propyl-9H-fluorene-9-carboxamide

30

To a solution of Part A(1) compound (911 mg, 2.21 mmol) in ethyl acetate (10 mL) at RT was added palladium on activated carbon (10%, 60 mg) under argon. The reaction was hydrogenated (balloon) at RT for 18 h. The reaction was filtered and the filtrate was evaporated to give 720 mg of a white solid. A portion of the product (500 mg) was

35

recrystallized from ethyl acetate/hexane to give title compound (350 mg, 60%) as a white solid.

m.p. 138-140°C.

5 MS (CI, + ions) m/z 385 (M+H).

Anal. Calc. for $C_{26}H_{28}N_2O \cdot 0.3H_2O$:

C, 80.09; H, 7.39; N, 7.18

Found: C, 80.01; H, 7.31; N, 7.17.

10

B. 9-[3-[4-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-phenyl]propyl]-N-propyl-9H-fluorene-9-carboxamide

Following the procedure in Example 194 Part

15 A compound (360 mg, 0.94 mmol) was reacted with phthalic anhydride (140 mg, 0.94 mmol) to give 450 mg of a colorless oil. The product was crystallized from MeOH/H₂O to give title compound (380 mg, 79%) as a white solid.

20

m.p. 148-151°C.

MS (CI, + ions) m/z 515 (M+H).

Anal. Calc. for $C_{34}H_{30}N_2O_3 \cdot 0.9H_2O$:

25 C, 76.93; H, 6.04; N, 5.28

Found: C, 76.88; H, 5.73; N, 5.23.

Example 208

9-[3-[4-(Benzoylamino)]phenyl]-N-propyl-9H-fluorene-9-carboxamide

30

To a solution of Example 207 Part A compound (100 mg, 0.26 mmol) and triethylamine (0.04 mL, 0.39 mmol) in dichloromethane at 0°C was added dropwise a solution of benzoyl chloride (0.04 mL, 0.31 mmol) in dichloromethane (1 mL). The reaction was stirred at 0 °C for 20 min. Ethyl acetate (50 mL) was added and the solution was

35

washed with saturated sodium bicarbonate solution
(2 x 30 mL), water (2 x 30 mL), brine (2 x 30 mL)
and dried over MgSO_4 . Purification was performed
by flash chromatography on silica gel (50 g),
5 loaded and eluted with 30% ethyl acetate in hexane.
Pure fractions were combined and evaporated to give
a solid. The resulting solid was recrystallized
from ethyl acetate/hexane to give title compound
(52 mg, 41%) as a white solid.

10

m.p. 187-190°C.

MS (CI, + ions) m/z 489 (M+H).

Anal. Calc. for $\text{C}_{33}\text{H}_{32}\text{N}_2\text{O}_2 \cdot 1.0 \text{ H}_2\text{O}$:

15 C, 78.23; H, 6.76; N, 5.53

Found: C, 78.44; H, 6.54; N, 5.43.

Example 209

9-[3-[(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)phenyl]-
20 propyl]-N-propyl-9H-fluorene-9-carboxamide

Following the procedure in Example 194,
Example 207 Part (A2) compound (350 mg, 0.68 mmol)
was reacted to give 300 mg of a colorless oil. The
product was crystallized from MeOH/ H_2O to give
25 title compound (160 mg, 47%) as a white solid.

m.p. 122-125°C.

MS (CI, + ions) m/z 501 (M+H).

30 Anal. Calc. for $\text{C}_{34}\text{H}_{32}\text{N}_2\text{O}_2 \cdot 0.8\text{H}_2\text{O}$:

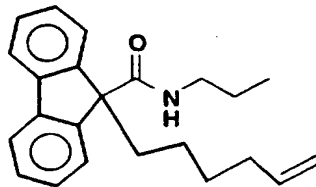
C, 79.29; H, 6.58; N, 5.44

Found: C, 79.28; H, 6.51; N, 5.29.

Example 210

9-[5-[(6-Ethoxy-2-benzothiazolyl)thio]pentyl]-N-propyl-9H-fluorene-9-carboxamide

A.



5

To a mixture of 3.0 g (11.95 mmol) of Example 11 Part C compound in 30 mL of THF, under argon at 0°C, was added 9.4 mL (23.90 mmol) of n-BuLi (2.5 M in hexanes) dropwise. The dianion was stirred for 0.5 h at which time 1.9 mL (14.34 mmol) of 6-bromo-1-hexene (Aldrich) was added dropwise. The reaction gradually warmed to RT and was stirred for 6 days. The reaction was diluted with a 1:1 mixture of ethyl acetate/water and separated. The organics were washed with brine, dried (Na₂SO₄) and evaporated. Flash chromatography was performed on 200g of silica gel eluting with 4:1 hexanes/ethyl acetate to provide 3.0 g (77%) of title compound as a pale yellow solid.

mp 54-56°C.

TLC Silica gel (4:1 hexanes/ethyl acetate) R_f=0.27.MS (CI-NH₃, + ions) m/e 334 (M+H).

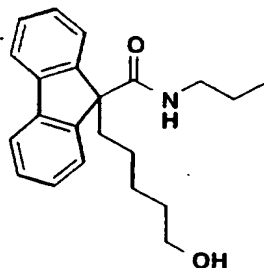
25

Anal. Calc. for C₂₃H₂₇NO:

C, 82.84; H, 8.16; N, 4.20

Found: C, 82.90; H, 8.18; N, 4.59.

B.



To a solution of 2.0 g (6.00 mmol) of Part
5 A compound in 20 mL of methanol, under nitrogen at
-78°C, was bubbled O₃ for 0.5 h. The solution was
purged with nitrogen and treated with 718 mg (18.89
mmol) of sodium borohydride (~ 5 pellets). The
mixture was gradually warmed to room temperature
10 and was stirred for 18 h, at which time the
reaction was diluted with ether and quenched with
NH₄Cl. The organics were washed with water, brine,
dried (Na₂SO₄) and evaporated. Flash
chromatography was performed on 200 g of silica gel
15 eluting with 1:1 hexanes/ethyl acetate to provide
1.6 g (80%) of title compound as a colorless oil.

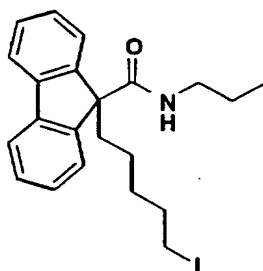
TLC Silica gel (1:1 hexanes/ethyl acetate) R_f=0.13.

20 Anal. Calcd. for C₂₂H₂₇NO₂ + 0.40 mol H₂O + 0.15
mol CH₂Cl₂.

C, 74.44; H, 7.92; N, 3.92

Found: C, 74.50; H, 7.62; N, 3.73.

C.



To a solution of 1.4 g (4.15 mmol) of Part
5 B compound in 20 mL of THF, under argon at 0°C, was
added 620 mg (9.13 mmol) of imidazole and 1.4 g
(5.40 mmol) of triphenylphosphine. This mixture
was stirred at 0°C for 0.5 h, at which time 1.4 g
(5.40 mmol) of iodine in 10 mL of THF was added
10 dropwise. The reaction was stirred for 1.5 h, at
0°C, at which time it was diluted with hexanes and
washed with sodium bisulfite, NaHCO₃, brine, dried
(Na₂SO₄) and evaporated. Flash chromatography was
performed on 50 g of silica gel eluting with 1:1
15 hexanes/ethyl acetate to provide 1.57 g (84%) of
title compound as a white solid.

TLC: Silica gel (1:1 hexanes/ethyl acetate)

R_f = 0.63.

20 MS (ES, + ions) m/e 448 (M+H).

D. 9-[5-[(6-Ethoxy-2-benzothiazolyl)thio]-
pentyll]-N-propyl-9H-fluorene-9-carboxamide

To a solution of 200 mg (0.45 mmol) of Part
25 C compound in 5 mL of DMF, under argon at RT, was
added 125 mg (0.90 mmol) of K₂CO₃ followed by 114
mg (0.54 mmol) of 6-ethoxy-2-mercaptobenzothiazole.
The reaction was stirred for 18 h at which time it
was diluted with ether and the organics were washed
30 with water, brine, dried (Na₂SO₄) and evaporated.
Flash chromatography was performed on 50 g of
silica gel eluting with 95:5

dichloromethane/isopropanol to provide 120 mg (50%) of title compound as a biege solid.

mp 67-70°C .

5 TLC Silica gel (95:5 dichloromethane/isopropanol)

R_f = 0.35.

MS (CI-NH₃, + ions) m/e 531 (M+H).

Anal. Calcd. for C₃₁H₃₄N₂O₂S₂:

10 C, 70.15; H, 6.46; N, 5.28; S, 12.08

Found: C, 69.95; H, 6.20; N, 5.22; S, 12.11.

Example 211

9-[4-[4-(Benzoylamino)phenyl]butyl]-N-propyl-9H-
15 fluorene-9-carboxamide

Benzoyl chloride (156 µL, 1.35 mmol) was added dropwise to a solution of Example 207 Part A compound (490 mg, 1.23 mmol) and triethylamine (257
20 µL, 1.85 mmol) in CH₂Cl₂ (4 mL) at 0°C under argon. The reaction was stirred at 0°C for 30 min, diluted with CH₂Cl₂ (20 mL) and CHCl₃ (20 mL), washed with 1N KOH (2 x 10 mL) and water (10 mL), then dried
25 over MgSO₄. Evaporation gave a yellow solid, which was adsorbed onto silica gel (10 g), then purified by flash chromatography on silica gel (150 g) eluting with 5% EtOAc/CH₂Cl₂ to give a solid. The product was dried under high vacuum at 50°C
30 overnight to provide title compound (412 mg, 67%) as a white solid.

mp 171-173°C.

Anal. Calcd. for C₃₄H₃₄N₂O₂ • 0.4 H₂O:

35 C, 81.24; H, 6.82; N, 5.57

Found: C, 80.88; H, 6.83; N, 5.33.

Example 2129-[5-(Dibutoxyphosphinyl)pentyl]-N-propyl-9H-fluorene-9-carboxamide

5 To 400 mg (0.89 mmol) of Example 209 Part A compound, under argon, was added 1.2 mL (4.45 mmol) of tributylphosphite (neat). The mixture was heated to 120°C for 18 h and bulb to bulb distilled (5 mm, 100°C) to remove lower boiling impurities
10 and provide a pale yellow oil. Flash chromatography was performed on 75 g of silica gel eluting with 95:5 dichloromethane/isopropanol to provide 440 mg (96%) of title compound as a pale yellow oil.

15 TLC Silica gel (95:5 dichloromethane/isopropanol)
R_f = 0.29.

IR 3434, 2959, 2934, 2872, 1665, 1508, 1449, 1244,
20 1024, 978, 743 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) is consistent with the indicated compound.

25 MS (CI-NH₃, + ions) m/e 514 (M+H).

Anal. Calcd. for C₃₀H₄₄NO₄P:

C, 70.15; H, 8.63; P, 6.03

Found: C, 70.60; H, 8.80; P, 5.86.

30 ¹³C NMR (75 MHz, CDCl₃) is consistent with the indicated compound.

35 The following compounds were prepared employing procedures as described hereinbefore.

Example 213

N,N-Diethyl-9-(2-propenyl)-9H-fluorene-9-carboxamide

- 5 MS (CI, M+H)⁺ m/z 306
Anal. Calcd for C₂₁H₂₃NO•0.14 H₂O:
C, 81.90; H, 7.62; N, 4.55
Found: C, 82.11; H, 7.52; N, 4.34.
mp 84-86°C.

10

Example 214

N-Ethyl-9-propyl-9H-fluorene-9-carboxamide

- MS (CI, M+H)⁺ m/z 280
15 Anal. Calcd for C₁₉H₂₁NO:
C, 81.68; H, 7.58; N, 5.01
Found: C, 81.45; H, 7.77; N, 5.06.
mp 96-97.5°C.

20

Example 215

N-Ethyl-9-(2-propenyl)-9H-xanthene-9-carboxamide

- MS (CI-NH₃, + ions) m/e 311 (M+NH₄), 294 (M+H).
Anal. Calcd for C₁₉H₁₉O₂N:
25 C, 77.79; H, 6.53; N, 4.77
Found: C, 77.87; H, 6.57; N, 4.77.
mp 111-112°C.

Example 216N-Ethyl-9-(3-phenylpropyl)-9H-xanthene-9-carboxamide

5 MS (CI-NH₃, + ions) m/e 372 (M+H).

Anal. Calcd for C₂₅H₂₅NO₂:

C, 80.83; H, 6.78; N, 3.77

Found: C, 80.77; H, 6.88; N, 3.83.

mp 130°C.

10

Example 2179-[(4-Morpholinyl)carbonyl]-9-propyl-9H-fluorene

CI-Mass Spec. (M+H)=322.

15 Anal. Calcd for C₂₁H₂₃NO₂:

C, 78.47; H, 7.21; N, 4.36

Found: C, 78.43; H, 7.11; N, 4.18.

mp 92-94°C.

20

Example 2189-Hexyl-N-propyl-9H-xanthene-9-carboxamide

MS (CI-NH₃, + ions) m/e 352 (M+H).

Anal. Calcd for C₂₃H₂₉NO₂:

25 C, 78.60; H, 8.32; N, 3.98

Found: C, 78.64; H, 8.46; N, 3.96.

mp 76-77.5°C.

Example 219

30 N-Methoxy-N-methyl-9-propyl-9H-fluorene-9-carboxamide

CI-Mass Spec. (M+H)=296.

Anal. Calcd for C₁₉H₂₁NO₂:

35 C, 77.26; H, 7.17; N, 4.74

Found: C, 77.12; H, 7.04; N, 4.68.

mp 73.75°C.

Example 220

10,11-Dihydro-5-(3-phenyl-2-propenyl)-N-propyl-5H-dibenzo[a,d]cycloheptene-5-carboxamide

5

MS (CI-NH₃, + ions) m/e 396 (M+H).

Anal. Calcd for C₂₈H₂₉NO:

C, 85.02; H, 7.39; N, 3.54

Found: C, 84.66; H, 7.46; N, 3.46.

10 mp 159°C.

Example 221

N-Methyl-9-propyl-9H-fluorene-9-carboxamide

15 CI-Mass Spec. (M+H)=266.

Anal. Calcd for C₁₈H₁₉NO+0.12 H₂O:

C, 80.82; H, 7.25; N, 5.24

Found: C, 80.90; H, 7.26; N, 5.16.

mp 145-146°C.

20

Example 222

1-(9-Propyl-9H-fluoren-9-yl)-1-pentanone

CI-Mass Spec. (M+H)=293.

25 Anal. Calcd for C₂₁H₂₄O:

C, 86.20; H, 8.24

Found: C, 85.86; H, 8.14.

mp 56-58°C.

30

Example 223

α-Butyl-9-propyl-9H-fluorene-9-methanol

CI-Mass Spec. (M+NH₄)=312⁺.

Anal. Calcd for C₂₁H₂₆O+0.12 H₂O:

35 C, 85.05; H, 8.92

Found: C, 85.05; H, 8.87.

mp 88-90°C.

Example 2241-(9-Propyl-9H-fluoren-9-yl)-1-butanone

- 5 CI-Mass Spec. (M+H)=279.
Anal. Calcd for C₂₀H₂₂O+0.1 H₂O:
C, 85.79; H, 7.98
Found: C, 85.79; H, 8.15.
mp 65-67°C.

10

Example 225 α ,9-Dipropyl-9H-fluorene-9-methanol

- CI-Mass Spec. (M+NH₃)=298.
15 Anal. Calcd for C₂₀H₂₄O+0.1 H₂O:
C, 85.15; H, 8.64
Found: C, 85.15; H, 8.72.
mp 83-85°C.

20

Example 22610,11-Dihydro-5-(2-propenyl)-N-propyl-5H-dibenzo-
[a,d]cycloheptene-5-carboxamide

- MS (CI-NH₃, + ions) m/e 320 (M+H).
25 Anal. Calcd for C₂₂H₂₅NO:
C, 81.98; H, 7.92; N, 4.35
Found: C, 82.01; H, 7.91; N, 4.32.
mp 76-79°C.

Example 2279-(3-Phenylpropyl)-N-propyl-9H-thioxanthene-9-carboxamide

5 MS (CI-NH₃, + ions) m/e 402 (M+H).

Anal. Calcd for C₂₆H₂₇NOS:

C, 77.77; H, 6.78; N, 3.49

Found: C, 77.60; H, 6.83; N, 3.42.

mp 130-131°C.

10

Example 228N,9-Dipropyl-9H-thioxanthene-9-carboxamide

MS (CI-NH₃, + ions) m/e 326 (M+H).

15 Anal. Calcd for C₂₀H₂₃NOS:

C, 73.81; H, 7.12; N, 4.30

Found: C, 73.84; H, 7.36; N, 4.24.

mp 132-133°C.

20

Example 22910,11-Dihydro-5-(3-phenylpropyl)-N-propyl-5H-dibenzo-[a,d]cycloheptane-5-carboxamide

MS (CI, NH₃, + ions) m/z 398 (M+H).

25 Anal. Calcd for C₂₈H₃₁NO+0.4 H₂O:

C, 82.90; H, 7.93; N, 3.45

Found: C, 82.99; H, 7.95; N, 3.36.

mp 109-112°C.

30

Example 230(E)-2,7-Difluoro-9-(3-phenyl-2-propenyl)-N-propyl-9H-fluorene-9-carboxamide

MS (CI, M+H)⁺ m/z 404.

35 Anal. Calcd for C₂₆H₂₃NF₂O:

C, 77.40; H, 5.75; N, 3.47

Found: C, 77.32; H, 5.70; N, 3.33.

mp 124-126°C.

Example 231

9-(3-Phenylpropyl)-N-(2-pyridinylmethyl)-9H-
5 fluorene-9-carboxamide

CI-Mass Spec. (M+H)=419.

Anal. Calcd for C₂₉H₂₆N₂O:

C, 83.22; H, 6.26; N, 6.70

10 Found: C, 83.42; H, 6.31; N, 6.62.

mp 115-116°C.

Example 232

2,7-Difluoro-9-(3-phenylpropyl)-N-propyl-9H-
15 fluorene-9-carboxamide

MS (CI, M+H)⁺ m/z 406.

Anal. Calcd for C₂₆H₂₅F₂NO•0.12 H₂O:

C, 76.62; H, 6.24; N, 3.44; F, 9.32

20 Found: C, 76.64; H, 6.33; N, 3.42; F, 9.12.

mp 99-100.5°C.

Example 233

2,7-Difluoro-9-(3-phenylpropyl)-N-(4-pyridinyl-
25 methyl)-9H-fluorene-9-carboxamide

MS (electrospray, M+H)⁺ m/z 455⁺.

Anal. Calcd for C₂₉H₂₄N₂F₂O•0.25 H₂O:

C, 75.88; H, 5.38; N, 6.10

30 Found: C, 75.93; H, 5.15; N, 6.04.

mp 60-62°C.

Example 234

9-(Butylthio)-9-propyl-9H-fluorene
35 9-(Butylthio)-9-propyl-9H-fluorene

MS (CI-NH₃, + ions) m/e 297 (M+H), 207 (M+H-
C₄H₁₀S).

Anal. Calcd for $C_{20}H_{24}S$:

C, 81.03; H, 8.16; N, 10.81

Found: C, 81.40; H, 8.47; N, 10.85.

5

Example 235

9-(Butylsulfinyl)-9-propyl-9H-fluorene

MS (ES, + ions) m/e 625 (2M+H), 313 (M+H).

Anal. Calcd for $C_{20}H_{24}SO$:

10

C, 76.88; H, 7.74; N, 10.26

Found: C, 77.12; H, 7.78; N, 9.93.

mp 57-59°C.

Example 236

15 9-(4-Hydroxybutyl)-N-propyl-9H-fluorene-9-carboxamide

MS (CI-NH₃, + ions) m/e 324 (M+H).

Anal. Calcd for $C_{21}H_{25}NO_2$:

20

C, 77.99; H, 7.79; N, 4.33

Found: C, 77.89; H, 7.92; N, 4.35.

mp 73-75°C.

Example 237

25 9-[4-(Phenylthio)butyl]-N-propyl-9H-fluorene-9-carboxamide

MS (CI-NH₃, + ions) m/e 416 (M+H).

Anal. Calcd for $C_{27}H_{29}NOS$:

30

C, 78.03; H, 7.03; N, 3.37; S, 7.71

Found: C, 77.70; H, 7.26; N, 3.35; S, 7.51.

mp 50-53°C.

Example 238

9-[3-(1,3-Dioxan-2-yl)propyl]-N-propyl-9H-fluorene-
9-carboxamide

- 5 MS (CI-NH₃, + ions) m/e 380 (M+H).
Anal. Calcd for C₂₄H₂₉NO₃ + 0.32 mol H₂O:
C, 74.82; H, 7.75; N, 3.64
Found: C, 74.75; H, 7.33; N, 3.64.
mp 127-128°C.

10

Example 239

9-[3-(1,3-Dioxolan-2-yl)propyl]-N-propyl-9H-
fluorene-9-carboxamide

- 15 MS (CI-NH₃, + ions) m/e 366 (M+H).
Anal. Calcd for C₂₃H₂₇NO₃:
C, 75.59; H, 7.45; N, 3.83
Found: C, 75.23; H, 7.63; N, 3.76.
mp 88-90°C.

20

Example 240

cis-N,9-Dipropyl-1H-thioxanthene-9-carboxamide, 10-
oxide

- 25 MS (CI-NH₃, + ions) m/e 342 (M+H).
Anal. Calcd for C₂₀H₂₃NO₂S:
C, 70.35; H, 6.79; N, 4.10
Found: C, 70.25; H, 6.86; N, 4.10.
mp 201-204°C.

30

Example 241

5-(2-Propenyl)-N-propyl-5H-indeno[1,2-b]pyridine-5-
carboxamide

- 35 MS (CI, M+H)⁺ m/z 293⁺.

Anal. Calcd for $C_{19}H_{20}N_2O \cdot 0.1 H_2O$:

C, 77.58; H, 6.92; N, 9.52

Found: C, 77.50; H, 6.84; N, 9.57.

mp 131-133.5°C.

5

Example 242

(E)-5-(3-Phenyl-2-propenyl)-N-propyl-5H-indeno[1,2-b]pyridine-5-carboxamide

10 mp 153-154.5

MS (CI, M+H)⁺ m/z 369⁺.

Anal. Calcd for $C_{25}H_{24}N_2O$:

C, 80.32; H, 6.63; N, 7.49

Found: C, 80.26; H, 6.51; N, 7.55.

15

Example 243

N-Ethyl-N-methyl-9-(2-propenyl)-9H-fluorene-9-carboxamide

20 MS (CI, M+H)⁺ m/z 292.

Anal. Calcd for $C_{20}H_{21}NO \cdot 0.06$ dioxane:

C, 81.94; H, 7.30; N, 4.72

Found: C, 81.76; H, 7.39; N, 4.68.

25

Example 244

N,9-Dipropyl-9H-thioxanthene-9-carboxamide, 10,10-dioxide

MS (CI-NH₃, + ions) m/z 380 (M+Na) 375 (M+NH₄), 358 (M+H).

30

Anal. Calcd for $C_{20}H_{23}NO_3S + 0.6 CH_2Cl_2$:

C, 60.58; H, 5.97; N, 3.43

Found: C, 60.58; H, 5.79; N, 3.39.

mp 264-266°C.

35

Example 245

trans-N,9-Dipropyl-9H-thioxanthene-9-carboxamide,
10-oxide

- 5 MS (CI-NH₃, + ions) m/z 342 (M+H).
Anal. Calcd for C₂₀H₂₃NO₂S + 0.4 H₂O:
C, 68.92; H, 6.88; N, 4.02
Found: C, 68.96; H, 7.18; N, 3.98.
mp 147-150°C.

10

Example 246

9-[3-(Dibutoxyphosphinyl)propyl]-N-(2-pyridinyl-
methyl)-9H-fluorene-9-carboxamide

- 15 CI-Mass Spec. (M+H)=535.
Anal. Calcd for C₃₁H₃₉N₂PO₄•0.5 H₂O:
C, 68.48; H, 7.42; N, 5.15; P, 5.70
Found: C, 68.28; H, 7.23; N, 5.28; P, 5.50.

20

Example 247

1-(9-Propyl-9H-fluorene-9-yl)-2-(1-piperidinyl)-
ethanone, monohydrochloride

- MS (ES) 334 (M+H).
25 Anal. Calcd for C₂₃H₂₈ClNO • H₂O:
C, 71.21; H, 7.79; N, 3.61
Found: C, 71.01; H, 7.75; N, 3.93.

Example 248

- 30 N-(5-Hydroxypentyl)-9-propyl-9H-fluorene-9-
carboxamide
-

- MS (CI, + ions) m/z 338 (M+H).
Anal. Calcd for C₂₂H₂₇NO₂ + 0.3 H₂O:
35 C, 77.13; H, 8.11; N, 4.09
Found: C, 77.10; H, 8.23; N, 4.00.
mp 48.51°C.

Example 249

9-(3-Cyanopropyl)-N-propyl-9H-fluorene-9-carboxamide

5

MS (ES, + ions) m/z 319 (M+H).

Anal. Calcd for C₂₁H₂₂N₂O:

C, 79.21; H, 6.96; N, 8.80

Found: C, 78.98; H, 6.89; N, 8.68.

10 mp 80-83°C.

Example 250

N-[[4-[[[(9-Propyl-9H-fluoren-9-yl)carbonyl]amino]-phenyl]methyl]-9-propyl-9H-fluorene-9-carboxamide

15

MS (CI, + ions) 591 (M+H).

Anal. Calcd for C₄₁H₃₈N₂O₂ • 0.3 H₂O:

C, 82.60; H, 6.53; N, 4.70

Found: C, 82.62; H, 6.44; N, 4.64.

20 mp 188-190°C.

Example 251

N-[4-(4-Aminophenyl)methyl]-9-propyl-9H-fluorene-9-carboxamide

25

MS (ES, + ions) 357 (M+H).

Anal. Calcd for C₂₄H₂₄N₂O • 0.7 H₂O:

C, 78.10; H, 6.94; N, 7.59

Found: C, 78.26; H, 6.70; N, 7.48.

30 mp 96-99°C.

Example 252

9-[3-(Dibutoxyphosphinyl)propyl]-N-propyl-9H-fluorene-9-carboxamide

35

MS (CI-NH₃, + ions) m/e 486 (M+H).

Anal. Calcd for $C_{28}H_{40}NO_4P + 0.75 \text{ mol } H_2O$:

C, 67.37; H, 8.38; N, 2.81; P, 6.21

Found: C, 67.49; H, 8.28; N, 2.69; P, 6.45.

5

Example 253

4-(1-Piperidinyl)-1-(9-propyl-9H-fluoren-9-yl)-1-butanone, monohydrochloride

MS (ES) 362 (M+H).

10 Anal. Calcd for $C_{25}H_{32}ClNO$:

C, 75.45; H, 8.10; N, 3.52; Cl, 8.91

Found: C, 75.41; H, 8.18; N, 3.36; Cl, 8.72.

mp 148-150°C.

15

Example 254

N-Methyl-9-(3-phenylpropyl)-9H-fluorene-9-carboxamide

MS (CI, + ions) m/z 342 (M+H).

20 Anal. Calcd for $C_{24}H_{23}NO + 0.2 H_2O$:

C, 83.51; H, 6.84; N, 4.06

Found: C, 83.55; H, 6.69; N, 4.02.

mp 101-102°C.

25

Example 255

2-(Dimethylamino)-9-(3-phenylpropyl)-N-propyl-9H-fluorene-9-carboxamide

MS (CI, M+H)⁺ m/z 413⁺.

30 Anal. Calcd for $C_{28}H_{32}N_2O + 0.34 H_2O$:

C, 80.32; H, 7.87; N, 6.69

Found: C, 80.30; H, 7.74; N, 6.71.

Example 256

35 9-[4-(Dibutoxyphosphinyl)-2-butenyl]-N-propyl-9H-fluorene-9-carboxamide

MS (ES) 498 (M+H).

Anal. Calcd for $C_{29}H_{40}NO_4P$:

C, 70.00; H, 8.10; N, 2.81; P, 6.22

Found: C, 69.85; H, 8.15; N, 3.13; P, 6.19.

5

Example 257

9-[4-(4-Nitrophenyl)butyl]-N-propyl-9H-fluorene-9-carboxamide

10 MS (ES) 429 (M+H).

Anal. Calcd for $C_{27}H_{28}N_2O_3$:

C, 75.68; H, 6.59; N, 6.54

Found: C, 75.70; H, 6.58; N, 6.57.

mp 109-110°C.

15

Example 258

9-[3-(4-Nitrophenyl)-2-propenyl]-N-propyl-9H-fluorene-9-carboxamide

20 MS (CI, + ions) 413 (M+H).

Anal. Calcd for $C_{26}H_{24}N_2O_3 \cdot 0.3 H_2O$:

C, 74.73; H, 5.93; N, 6.70

Found: C, 74.54; H, 5.75; N, 6.67.

mp 143-146°C.

25

Example 259

5-(3-Phenylpropyl)-N-propyl-5H-indeno[1,2-b]pyridine-5-carboxamide

30 MS (CI, M+H)⁺ m/z 371⁺.

Anal. Calcd for $C_{25}H_{26}N_2O$:

C, 81.05; H, 7.07; N, 7.56

Found: C, 80.97; H, 7.12; N, 7.51.

mp 124.5-126°C.

35

Example 260

9-[4-(4-Aminophenyl)butyl]-N-propyl-9H-fluorene-9-carboxamide

5 MS (CI) 399 (M+H).

Anal. Calcd for $C_{27}H_{30}N_2O \cdot 0.3 H_2O$:

C, 80.28; H, 7.64; N, 6.93

Found: C, 80.37; H, 7.53; N, 7.34.

10

Example 261

9-[3-(4-Aminophenyl)propyl]-N-propyl-9H-fluorene-9-carboxamide

MS (CI, + ions) 385 (M+H).

15 Anal. Calcd for $C_{26}H_{28}N_2O \cdot 0.3 H_2O$:

C, 80.09; H, 7.39; N, 7.18

Found: C, 80.01; H, 7.31; N, 7.17.

mp 138-140°C.

20

Example 262

9-[4-(Dibutoxyphosphinyl)butyl]-9H-fluorene-9-carboxylic acid, methyl ester

MS (CI, + ions) m/z 473 (M+H).

25 Anal. Calcd for $C_{27}H_{37}O_5P$:

C, 68.63; H, 7.89; N, 6.55

Found: C, 68.37; H, 7.96; N, 6.21.

Example 263

30 N,N-Dibutyl-9-[(propylamino)carbonyl]-9H-fluorene-9-butanamide

MS (CI-NH₃, + ions) m/e 449 (M+H).

Anal. Calcd for $C_{29}H_{40}N_2O_2 + 0.29 \text{ mol } H_2O$:

35 C, 76.75; H, 9.01; N, 6.17

Found: C, 76.71; H, 8.92; N, 6.21.

mp 109-111°C.

Example 264

9-(5-Cyanopentyl)-N-propyl-9H-fluorene-9-carboxamide

5

MS (ES, + ions) m/e 347 (M+H).

Anal. Calcd for C₂₃H₂₆N₂O:

C, 79.73; H, 7.56; N, 8.09

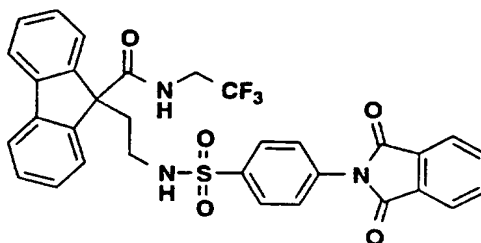
Found: C, 79.25; H, 7.55; N, 7.76.

10 mp 92-94°C.

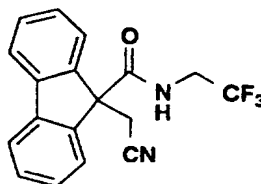
Example 265

9-[2-[[[4-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-phenyl]sulfonyl]amino]ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

15



A.



20

Butyllithium (18 mL, 2.5M in hexanes, 44 mmol) was added dropwise over 10 min to a solution of 9-fluorencarboxylic acid (4.2 g, 20 mmol) in THF (200 mL) at 0°C under argon. The slightly heterogeneous dark yellow reaction was stirred at 0°C for 30 min, then chloroacetonitrile (1.5 mL, 24 mmol) was added dropwise over 3 min. The orange reaction was stirred at 0°C for 30 min, warmed to RT and stirred for 3 h. The reaction was extracted

25

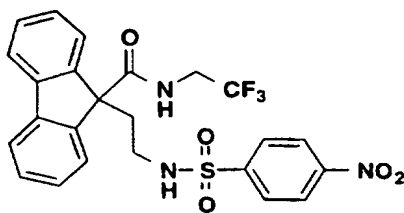
30

with water (2 x 100 mL) and the combined aqueous extracts were washed with Et₂O (100 mL). The aqueous layer was acidified to pH<2 with 1N HCl and extracted with CH₂Cl₂ (3 x 50 mL). The combined
5 organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo to give 4.7 g of a light yellow solid (mp 138-145°C).

A portion (2.63 g) of the crude carboxylic acid was dissolved in CH₂Cl₂ (30 mL) under argon.
10 N,N-Dimethylformamide (40 µL, 0.53 mmol) was added followed by oxalyl chloride (8.0 mL, 2.0M in CH₂Cl₂, 15.9 mmol). The reaction bubbled for a few minutes and was allowed to stir at RT for 1.5 h. The reaction was concentrated in vacuo then pumped
15 under high vacuum to give the crude acid chloride. Triethylamine (4.4 mL, 31.8 mmol) was added to a suspension of 2,2,2-trifluoroethylamine hydrochloride (1.71 g, 12.7 mmol) in CH₂Cl₂ (20 mL) at 0°C under argon. The resulting thick slurry was
20 stirred at 0 °C for 5 min, then a solution of the crude acid chloride in CH₂Cl₂ (10 mL) was added dropwise over 5 min. The reaction was stirred at 0°C for 10 min, diluted with CH₂Cl₂ (50 mL), washed with 1N HCl (2 x 20 mL) and saturated NaHCO₃ (30
25 mL), then dried over Na₂SO₄. Evaporation gave 3.5 g of a yellow foam which was purified by flash chromatography on silica (150 g) eluting with CH₂Cl₂ to give title compound (2.74 g, 76%) as a white solid (mp 159-159.5).

30

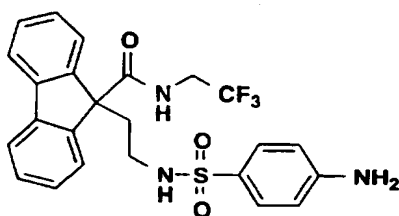
B.



Platinum (IV) oxide (107 mg, 0.472 mmol) was added to a solution of Part A compound (1.50 g, 4.72 mmol) and chloroform (750 μ L, 9.44 mmol) in MeOH (15 mL). The reaction mixture was
5 hydrogenated (balloon) at RT for 3.5 days, filtered through Celite, and concentrated in vacuo to provide 1.71 g of the crude amine hydrochloride.

To a solution of the crude amine hydrochloride and triethylamine (800 μ L, 5.80 mmol) in CH_2Cl_2 (7 mL) at 0°C under argon was added a
10 solution of 4-nitrobenzenesulfonyl chloride (612 mg, 2.77 mmol) (recrystallized from hexane prior to use) in CH_2Cl_2 (1 mL). The cloudy reaction was stirred at 0°C for 15 min, diluted with CH_2Cl_2 (10
15 mL), washed with saturated NaHCO_3 (2 x 5 mL), then dried over MgSO_4 . Evaporation gave 1.36 g of a yellow foam which was dissolved in 1:1 CH_2Cl_2 :30% EtOAc/hexane and purified by flash chromatography on silica (150 g) eluting with a step gradient of
20 30-50% EtOAc/hexane to give title compound (783 mg, 59%) as a white solid (mp 164.5-165.5).

C.



25

A mixture of Part B compound (760 mg, 1.46 mmol) and 10% palladium on carbon (77 mg, 0.073 mmol) in EtOAc (8 mL) was hydrogenated (balloon) at RT for 2.5 h, filtered through Celite with the aid
30 of EtOAc (50 mL), and concentrated in vacuo to provide title compound (728 mg, 100%) as a white foam. A sample of title compound was diluted with CH_2Cl_2 , concentrated in vacuo, and pumped under

high vacuum to give title compound as a white solid
(mp 184-186°C).

5 D. 9-[2-[[[4-(1,3-Dihydro-1,3-dioxo-2H-
isoindol-2-yl)-phenyl]sulfonyl]amino]
ethyl]-N-(2,2,2-trifluoroethyl)-9H-
fluorene-9-carboxamide

A solution of Part C compound (290 mg,
0.593 mmol) and phthalic anhydride (92 mg, 0.623
10 mmol) in N,N-dimethylacetamide (1 mL) was heated at
150°C under argon for 9 h, then cooled to RT. The
solvent was distilled off under high vacuum and the
amber oily residue was purified by flash
chromatography on silica gel (50 g) eluting with 5%
15 EtOAc/CH₂CH₂ to provide title compound (300 mg,
82%) as a white solid.

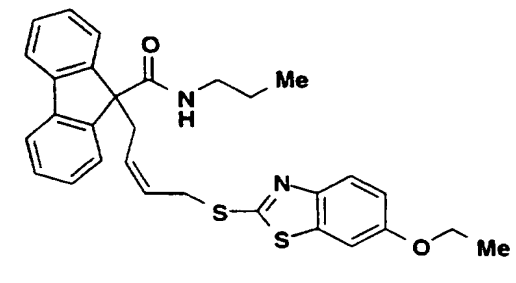
mp 235-237°C

Anal. Calcd. for C₃₂H₂₄F₃N₃O₅S • 0.4 H₂O:

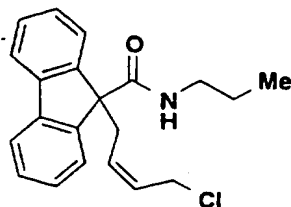
20 C, 61.31; H, 3.99; N, 6.78; F, 9.20; S,
5.17
Found: C, 61.37; H, 3.85; N, 6.64; F, 8.81; S,
5.36.

25 Example 266

(Z)-9-[4-[(6-Ethoxy-2-benzothiazolyl)thio]-2-
butenyl]-N-propyl-9H-fluorene-9-carboxamide



A.



Butyllithium (8.4 mL, 2.5M in hexane, 21
5 mmol) was added dropwise over 10 min to a solution
of 9-fluorencarboxylic acid (2.10 g, 10 mmol) in
THF (50 mL) at 0°C under argon. During addition of
the first equivalent of BuLi, the reaction became
thick with a white precipitate which became yellow
10 and cleared after addition of the second
equivalent. The reaction was stirred at 0°C for 20
min, then cis-1,4-dichloro-2-butene (1.2 mL, 11
mmol) was added dropwise over 5 min. The reaction
lightened in color during addition and was stirred
15 at 0°C for 3 h, then poured into 1N HCl (50 mL) and
extracted with CH₂Cl₂ (3 x 50 mL). The combined
organic layers were washed with brine (30 mL) then
dried over MgSO₄. Evaporation provided 3.5 g of a
yellow oil containing crystalline solid. The crude
20 residue was triturated with hexane (20 mL). The
supernatant was decanted, and the residue pumped
under high vacuum to give 2.93 g of a tan solid.

To a suspension of the crude acid prepared
above (1.42g, 4.77 mmol) and N,N-dimethylformamide
25 (5 drops) in CH₂Cl₂ (15 mL) at room temperature
under argon was added oxalyl chloride (3.6 mL, 2.0M
in CH₂Cl₂, 7.16 mmol). The reaction bubbled for 10
min, then the reaction was stirred at room
temperature for 1.5 h, at which time all solids had
30 dissolved. The reaction was concentrated in vacuo
to give an orange oil. The crude acid chloride was
dissolved in CH₂Cl₂ (15 mL) and cooled to 0°C.
Propylamine (1.2 mL, 14.3 mmol) was added dropwise
over 1 min, and the reaction was stirred at 0°C for

10 min. The reaction was partitioned between EtOAc (50 mL) and water (20 mL). The organic layer was washed with 1N HCl (2 x 20 mL) and brine (20 mL), then dried over MgSO₄. Evaporation gave 1.7 g of
5 an orange oil, which was purified by flash chromatography on silica gel (150 g) eluting with CH₂Cl₂ to give title compound (1.38 g, 84%) as a pale yellow oil.

10 B. (Z)-9-[4-[(6-Ethoxy-2-benzothiazolyl)-thio]-2-butenyl]-N-propyl-9H-fluorene-9-
carboxamide

To a solution of 500 mg (1.47 mmol) of Part A compound in 5 mL of DMF, under argon at RT, was
15 added 400 mg (2.94 mmol) of K₂CO₃ followed by 466 mg (2.20 mmol) of 6-ethoxy-2-mercaptobenzothiazole. The reaction was stirred for 5 h at RT, at which time it was heated to 50°C for 16 h. The reaction was diluted with ether and the organics were washed
20 with water (2x), brine, dried (Na₂SO₄) and evaporated. Flash chromatography was performed on 100 g of silica gel eluting with 3:2 hexanes/ethyl acetate to provide 450 mg (60%) of title compound as a beige solid.

25 mp 135-137°C.

Anal. Calcd. for C₃₀H₃₀N₂O₂S₂ + 0.55 mol H₂O:

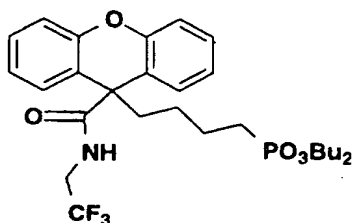
C, 68.68; H, 5.98; N, 5.34; S, 12.22

Found: C, 68.88; H, 5.77; N, 5.14; S, 12.26.

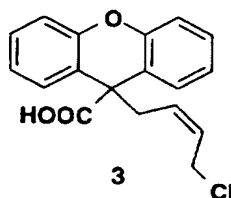
30

Example 267

9-[4-(Dibutoxyphosphinyl)butyl]-N-(2,2,2-trifluoro-
propyl)-9H-xanthene-9-carboxamide



A.

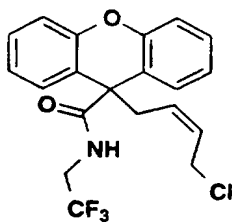


To a stirred solution of 5.00 g (22.1 mmol) of xanthene carboxylic acid in 100 mL of THF at 0°C was added 19.5 mL (48.7 mmol) of 2.5 M butyllithium in hexanes followed by 3.05 g (24.32 mmol) of cis-1,4-dichloro-2-butene. The reaction was allowed to stir at 0°C for 24 h when the mixture was diluted with 250 mL of ethyl acetate and 100 mL of 0.5 M HCl. The layers were separated, the organics dried (Na₂SO₄) and concentrated. The remainder was purified by flash column chromatography on silica gel (250 g) eluting with 30:70:0.5 ethyl acetate/hexanes/acetic acid to give 4.6 g (66%) of title compound as a white solid. mp 134-135°C.

15

20

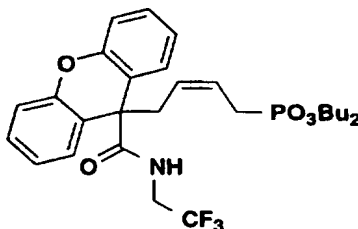
B.



To a stirred solution of 2.00 g (6.35 mmol) of Part A compound in 100 mL of dichloromethane at RT was added 3.6 mL (7.2 mmol) of 2M oxalyl chloride in dichloromethane followed by 2 drops of DMF. The reaction was allowed to stir at RT for 2.5 h when the solvent was evaporated and the semisolid residue pumped (≈ 1 mm pressure) for 0.5 h. The residue was dissolved by adding 300 mL of THF and cooled to 0°C. The mixture was treated with 0.9 g (7 mmol) of trifluoroethylamine hydrochloride and 1.41 g (14 mmol) of triethylamine and warmed to room temperature. The mixture was stirred overnight and diluted with 150 mL of ethyl acetate and 50 mL of 0.5 M HCl. The layers were separated, the organics dried (Na_2SO_4) and concentrated. The remainder was purified by trituration with hot methanol to give 1.30 g (52%) of title compound as a white solid. mp 153-159°C.

20

C.



A mixture of Part B compound (0.53 g, 1.34 mmol) and tributylphosphite (3.00 g, 12 mmol) was heated to 115-120°C for 24 h. The mixture was concentrated by bulb-to-bulb distillation to leave an amber colored oil. The remainder was purified by flash column chromatography on silica gel (60 g) eluting with 9:1 dichloromethane/acetone to give 0.65 g (86%) of title compound as a colorless oil.

30

TLC Silica gel (9:1 dichloromethane/acetone)

R_f = 0.4.

D. 9-[4-(Dibutoxyphosphinyl)butyl]-N-(2,2,2-trifluoropropyl)-9H-xanthene-9-carboxamide

A solution of Part C compound (0.60 g, 1.06 mmol) in ethanol (10 mL) was treated with 40 mg of 10% Pd/Carbon and placed under an atm of H₂ for 18 h. The mixture was diluted with 25 mL of ethanol and filtered through a pad of Celite. The filtrate was concentrated to an oil which gradually solidified to give 0.32 g (91%) of title compound as a colorless oil which gradually turned to a white solid on standing. mp 102-105°C.

Mass Spec. (ES, + ions) m/z 573 (M+NH₄), 556 (M+H)

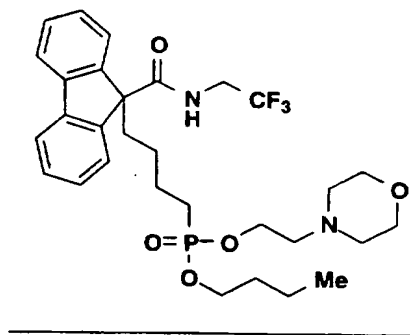
Anal. Calc'd for C₂₈H₃₇NO₅PF₃ + 0.65 H₂O:

C, 59.25; H, 6.81; N, 2.47; P, 5.46

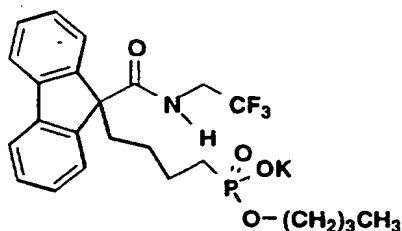
Found: C, 59.59; H, 6.53; N, 2.14; P, 5.03.

Example 268

9-[4-Butoxy[2-(4-morpholinyl)ethoxy]phosphinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



A.



To a solution of 1 g (1.85 mmol) of Example 186 compound in 10 mL of a 3:7 water/n-butanol solution was added 1 g (18.50 mmol) of KOH pellets. The mixture was heated to 100°C for 5 days, at which time it was evaporated to remove n-butanol and freeze dried. The residue was purified by MPLC on a column of CHP20P gel (2.5 cm diam. X 20 cm height) eluting with water (1 L) followed by a gradient created by the gradual addition of 500 mL of acetonitrile to a reservoir of 700 mL of water. Fractions #34 to 40 were pooled. The acetonitrile was removed under reduced pressure and the aqueous solution was freeze dried to provide 695 mg (72%) of title compound as a white lyophilate.

TLC: silica gel (8:1:1 n-propanol/water/aqueous NH₃) R_f=0.63.

MS (ES NH₄OH, + ions) m/z 525 (M+H+CH₃CN), 501 (M+NH₄), 484 (M+H).

Anal Calcd. for C₂₄H₂₈NO₄PF₃K + 0.93 H₂O:
 C, 53.56; H, 5.59; N, 2.60; P, 5.75
 Found: C, 53.60; H, 5.56; N, 2.56; P, 5.78.

B. 9-[4-Butoxy[2-(4-morpholinyl)ethoxy]-phosphinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

To a solution of 130 mg (0.25 mmol) of Part A compound in 3 mL of toluene, under argon at RT,

was added dropwise 35 μ L (0.25 mmol) of triethylamine followed by 95 μ L (0.75 mmol) of chlorotrimethyl silane. The reaction was stirred for 1 h at which time it was evaporated to dryness to provide a pale yellow solid. The solid was dissolved in 3 mL of dichloromethane, under argon at RT, and treated with two drops of DMF followed by the dropwise addition of 189 μ L (0.38 mmol) of oxalyl chloride (2.0 M in dichloromethane). The reaction was stirred for 0.5 h at which time it was evaporated to dryness to provide a yellow solid. The solid was dissolved in 5 mL of THF, under argon at RT, and treated dropwise with 46 μ L (0.38 mmol) of 4-(2-hydroxymethyl)morpholine. The reaction was stirred for 18 h at which time it was diluted with ether and washed with NaHCO_3 , brine, dried (Na_2SO_4) and evaporated. Flash chromatography was performed on 100 g of silica gel eluting with 9:1 dichloromethane/isopropanol to provide 120 mg (80%) of title compound as a colorless oil.

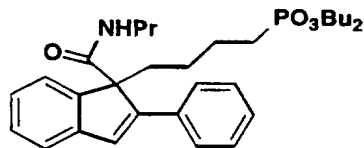
MS (ES, \pm ions) m/z 597 (M+H), 595 (M-H).

Anal. Calcd. for $\text{C}_{30}\text{H}_{40}\text{N}_2\text{O}_5\text{PF}_3$:

C, 60.39; H, 6.76; N, 4.70; F, 9.55

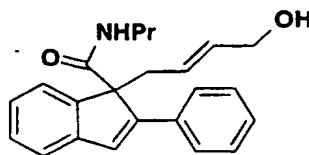
Found: C, 60.12; H, 6.45; N, 4.58; F, 9.59.

Example 269



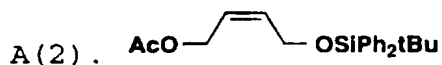
(where Pr is n-C₃H₇)

A.



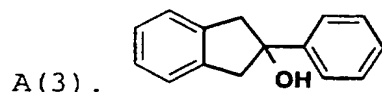
5

To a slurry of sodium hydride (6.975 g, 60% mineral oil dispersion, 0.174 mol) in 200 mL of THF at room temperature under argon was added cis-2-butene-1,4-diol (15.36 g, 0.174 mol) over 20 minutes. Gas evolved and a thick precipitate formed. The slurry was stirred for 16 h and then was rapidly treated with t-butyl diphenylchlorosilane (47.82 g, 0.174 mol). The reactions warmed to 40°C autogenously and a clear solution formed. After 15 min, the reaction was quenched with water and extracted twice with hexanes. The organic layers were combined, dried (Na₂SO₄) and evaporated. Purification by flash chromatography (12 x 30 cm column, dichloromethane) gave title compound as a colorless oil, 46.6 g, 82%.



To a stirred solution of Part A(1) compound (6.53 g, 20.0 mmol) and triethylamine (3.53 mL, 25.3 mmol) in 50 mL of dichloromethane at room temperature under argon was added acetic anhydride (2.4 mL, 22.5 mmol) and DMAP (20 mg, 0.16 mmol). After 2h, TLC indicated that no alcohol remained. The reaction was evaporated at less than 30°C and the residue partitioned between 10% citric acid and hexanes. The organic layer was washed with water and saturated sodium bicarbonate solution, dried (Na₂SO₄) and evaporated. The isolated colorless

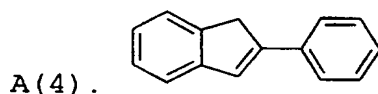
oil, title compound (7.02 g, 95%), was used without further purification.



5

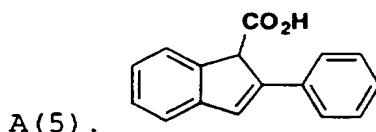
Anhydrous cerium chloride (16.00 g, 64.9 mmol) was stirred in an evacuated flask heated in an oil bath to 145°C for 2 h. The flask was flooded with argon, cooled to room temperature and then to 0°C in an ice bath. To this powder was added 150 mL of THF. The stirred slurry was warmed to room temperature. After 14 h, the flask was again cooled to 0°C and phenylmagnesium chloride solution (21.2 mL, 63.6 mmol, 3 M in ether) was added. The resulting yellow slurry was stirred for 1.5 h and then a solution of 2-indanone (Aldrich, purified by flash chromatography) (5.45 g, 41.2 mmol, freshly chromatographed) was added. After 30 min, the reaction mixture was quenched with 10% citric acid and extracted twice with ether. The organic extracts were dried (MgSO₄) and evaporated. Purification by flash chromatography (5 x 20 cm column, 17:3 dichloromethane/hexanes) gave title compound as a colorless oil, 6.66 g, 77%.

25



To Part A(3) compound (neat) (6.40 g, 30.4 mmol) was added potassium bisulfate (6.4 g, 47 mmol). The mixture was stirred under argon and placed in an oil bath heated to 160°C for 20 min. The resulting solid mass was cooled, partitioned between dichloro-methane and water. The organic layer was dried (MgSO₄) and evaporated to provide title compound (5.84 g, 100%) as a white solid, mp

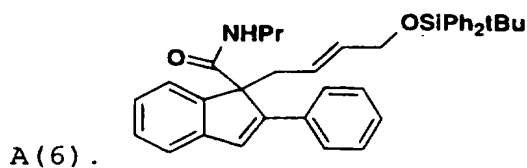
163-164°C. The compound was used in subsequent reactions without further purification.



5

To a solution of Part A(4) compound (1.481 g, 7.70 mmol) in 20 mL of THF at 0°C under argon was added n-butyllithium (3.0 mL, 7.50 mmol, 2.5 M in hexanes) over 10 min. The resulting deep orange solution was stirred for 1h. The reaction was quenched with several small pieces of THF-washed dry ice. The resulting thick yellow slurry was stirred for 1 h and then treated with 20 mL of 2 M potassium hydroxide solution. This solution was extracted twice with ether and the aqueous residue was brought to pH 2 with 3 N sulfuric acid. The mixture was extracted three times with ethyl acetate, the extracts combined, dried (MgSO₄) and evaporated to give title compound as a light yellow powder (1.50 g, 82%), mp 212-215°C. The compound was used in subsequent reactions without further purification.

25

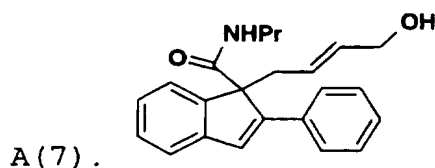


A mixture of Part A(5) compound (890 mg, 3.77 mmol), Part A(2) compound (2.55 g, 3.77 mmol) and triphenylphosphine (190 mg, 0.724 mmol) was evaporated twice from toluene. The mixture was dissolved in 20 mL of THF, stirred under argon and treated with bis(trimethylsilyl)acetamide (BSA) (3.7 mL, 15 mmol). After 30 min, tetrakis-(triphenylphosphine)palladium(0) (430 mg, 0.39

mmol) was added and the reaction set to reflux. After 16h, the orange solution was cooled, evaporated and re-evaporated twice from methanol. The gummy residue was dissolved in ether and washed
5 once with 10% citric acid. The organic extract was dried (MgSO_4), evaporated and re-evaporated once from toluene.

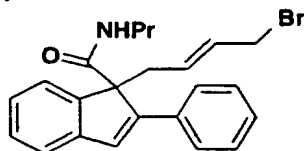
To a stirred solution of this product in 10 mL of dichloromethane under argon at room
10 temperature was added oxalyl chloride (0.9 mL, 7.0 mmol) and then DMF (0.05 mL). After 1 h, the reaction was evaporated to give an orange oil which was dissolved in 10 mL of THF.

This solution was added to a stirred
15 solution of n-propylamine (1.4 mmol, 16 mmol) in 10 mL of THF at 0 °C over 10 min. After 1h, the reaction mixture was diluted with ether and washed once with 10% citric acid. The organic extract was dried (MgSO_4) and evaporated. Purification by
20 flash chromatography (5 x 20 cm column, dichloromethane) gave title compound as an orange oil, 1.50 g, 77%.



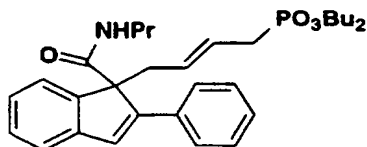
To a stirred solution of Part A(6) compound (2.15 g, 4.18 mmol) in 15 mL of THF at room temperature under argon was added tetrabutyl-ammonium fluoride (10 mL, 10 mmol, 1 M in THF).
30 After 1h, the reaction was quenched with brine and extracted three times with ethyl acetate. The organic extract was dried (MgSO_4) and evaporated. Purification by flash chromatography (5 x 15 cm column, 3:2 hexanes/ethyl acetate) gave title
35 compound as a colorless glass, 1.09 g, 75%.

B.



5 To a solution of 400 mg (1.15 mmol) of Part A compound and 600 mg (2.3 mmol) of triphenylphosphine in 4 mL of THF at room temperature under argon was added 763 mg (2.3 mmol) of tetrabromomethane. After two hours, the reaction mixture was
 10 evaporated at less than 25 °C. Purification by flash chromatography on silica gel (2.5 x 15 cm column, dichloromethane) gave title compound as a white solid, mp 82-84 °C, 440 mg, 95%.

15 C.



A stirred solution of Part B compound (350 mg, 0.853 mmol) in 2 mL of tributyl phosphite was
 20 heated to 110°C under argon for two hours. The reaction mixture was subjected to bulb-to-bulb distillation at 0.5 mm Hg and 100°C to remove excess tributylphosphite. The residue was purified by flash chromatography on silica gel
 25 (2.5 x 15 cm column, 2:1 ethylacetate/hexanes) to give title compound as a colorless oil, 425 mg, 95%.

MS (electrospray, + ions) m/e 524 (M+H), 541 (M+NH₄)

Anal. Calc'd for C₃₁H₄₂NO₄P•0.19 H₂O:

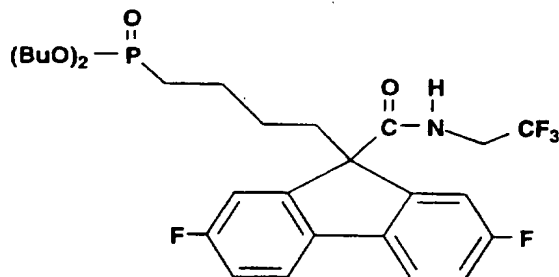
C, 70.64; H, 8.10; N 2.66; P, 5.88

Found: C, 70.64; H, 8.11; N 2.56; P, 6.18.

Example 270

9-[4-(Dibutoxyphosphinyl)butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

5



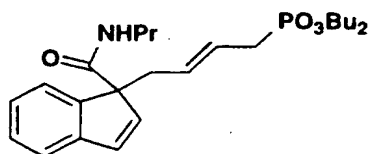
A solution of Example 203 compound (574 mg, 1 mmol) in 25 ml of absolute ethanol containing 250 mg of 10% Pd on carbon as catalyst was stirred under a hydrogen atmosphere (balloon) for 48 hours. The reaction was filtered after stirring 24 hrs and fresh catalyst added. The reaction was filtered through a 0.45 μ m nylon filter and the solvent evaporated yielding 538 mg (94%) of title compound as a colorless oil.

Mass Spec (CI) • m/z 576 (M+H).

Anal Calc'd for C₂₈H₃₅NF₅PO₄:

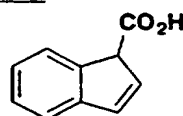
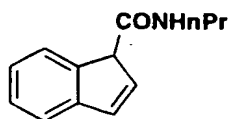
20 C, 58.43; H, 6.13; N, 2.43; F, 16.50; P, 5.38

Found: C, 58.54; H, 5.86; N, 2.39; F, 16.41; P, 5.39.

Example 271

5

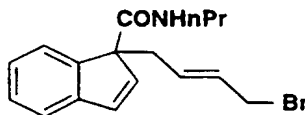
A.



To a stirred slurry of (3.20 g, 20.0 mmol) in 20 mL of dichloromethane at room temperature under argon was added 15.0 mL of oxalyl chloride (2 M in dichloromethane, 30.0 mmol) and 0.1 mL of DMF. The resulting yellow solution was stirred one hour and then evaporated at 25°C. The semi-solid residue was redissolved in 15 mL of THF and added drop-wise to a solution of n-propylamine (3.5 mL, 43 mmol) in 25 mL of THF at -10°C under argon. After one hour, the reaction mixture was partitioned between ethyl acetate and 10% citric acid solution. The organic extract was separated, dried (MgSO₄) and evaporated. Purification by flash chromatography on silica gel (5 x 20 cm column, 1:2 ethyl acetate/hexanes) gave title compound as a yellow solid, 2.36 g, 59%, mp 83-86°C.

25

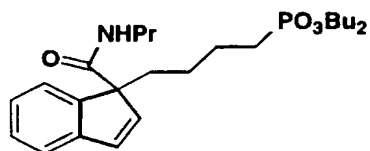
B.



To a stirred solution of Part A compound (1.28 g, 6.36 mmol) in 25 mL of THF under argon at

0°C was added 26.0 mL of potassium bis(trimethylsilyl)amide (0.5 M in toluene, 13.0 mmol) over 20 min. A deep purple solution formed. After 30 min, a solution of (E)-1,4-dibromobutene (4.0 g, 18.7 mmol, Aldrich) in 10 mL of THF was added over 10 min. After 30 min, the reaction mixture was partitioned between ethyl acetate and 1 M hydrochloric acid. The organic extract was separated, dried (MgSO₄) and evaporated. Purification by flash chromatography on silica gel (5 x 15 cm column, 19:81 ethyl acetate/hexanes) gave title compound as a colorless oil, 547 mg, 26%.

C.



15

A stirred solution of Part B compound (530 mg, 1.59 mmol) in 3.5 mL of tributyl phosphite was heated to 110°C under argon for 3 hours. The reaction mixture was subjected to bulb-to-bulb distillation at 0.5 mm Hg and 100°C to remove excess tributylphosphite. The residue was purified by flash chromatography on silica gel (2.5 x 15 cm column, 3:1 ethylacetate/hexanes) to give title compound, as a colorless oil, 565 mg, 79%.

Anal. Calc'd for C₂₅H₃₈NO₄P•0.25 H₂O:

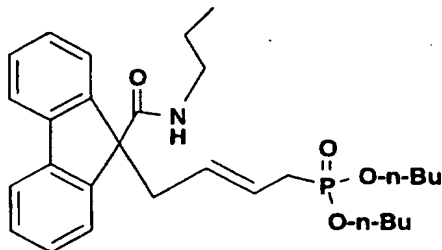
C, 66.42; H, 8.58; N 3.10; P, 6.85

Found: C, 66.43; H, 8.57; N 3.05; P, 6.90.

MS (electrospray, + ions) m/e 448.2 (M+H), 465.3 (M+NH₄).

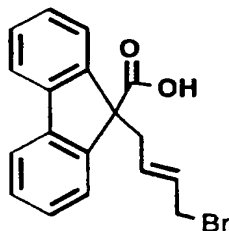
Example 272

(E)-9-[4-(Dibutoxyphosphinyl)-2-butenyl]-N-propyl-9H-fluorene-9-carboxamide



5

A.



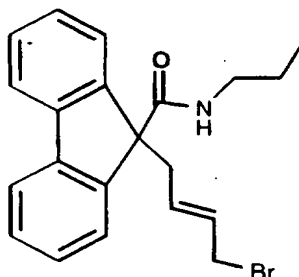
10 To a THF (150 ml) suspension of 9-fluorene-carboxylic acid (10 g, 0.048 mol) at 0°C under argon was added dropwise sodium bis(trimethylsilyl)amide (100 ml, 1 M in THF). After 30 min, 1,4-trans-2-butene (10.2 g, 0.048 mol) was added

15 and the reaction allowed to stir for 1 h. The reaction mixture was quenched with 1N HCl and the aqueous layer extracted 3 times with EtOAc. The combined organics were dried over Na₂SO₄ and evaporated in vacuo to give an oily-solid residue

20 (18 g). The residue was purified by flash column chromatography (SiO₂, 10 by 25 cm), eluting with 6.5% MeOH:CH₂Cl₂ to give title compound (2.48 g, 15% yield) as an oily solid. MS: (CI, M+NH₄⁺): m/z 360⁺.

25

B.



To a CH_2Cl_2 (30 ml) solution at 0°C of Part
5 A compound (2.48 g, 7.22 mmol) under argon was
added oxalyl chloride (1.46 g, 11.4 mmol) and DMF
(0.1 ml). The reaction mixture was stirred at room
temperature for 2.5 h and the volatiles were
removed *in vacuo*. The crude residue containing
10 acid chloride was co-evaporated with CH_2Cl_2 and
used directly in the following reaction.

To a THF (26 ml) solution of the acid
chloride (7.22 mmol) at 0°C under argon was added
n-propyl-amine (0.899 g, 15.2 mmol) and the
15 reaction was stirred for 1.45 h. After warming to
room temperature for 15 min, the mixture was stored
at -80°C overnight. The reaction mixture was
partitioned between EtOAc and water, the aqueous
layer extracted twice with EtOAc, the combined
20 organics washed with brine, dried over Na_2SO_4 , and
evaporated to give title compound (2.79 g, >100%
crude recovery, containing EtOAc) as a slightly
orange colored oil. MS: (CI, $\text{M}+\text{H}^+$): m/z 384 $^+$.

25 C. (E)-9-[4-(Dibutoxyphosphinyl)-2-
butenyl]-N-propyl-9H-fluorene-9-
carboxamide

A solution of Part B compound (977 mg, 2.54
mmol) and tri-*n*-butyl phosphite (2.75 ml) under
30 argon was heated at 120°C for 17 h. The volatiles
were removed *in vacuo* to give an oil (1.26 g).
The residue was purified by flash column

chromatography (SiO₂, 5 by 10 cm), eluting with
2.5% MeOH:CH₂Cl₂, to give after heating at 70°C in
vacuo overnight title compound (120 mg, 10% yield
from Part A compound) as a colorless oil. The bulk
5 of title compound was isolated as colorless oil
containing residual tri-*n*-butyl phosphite (1.07 g).
MS: (CI, M+H⁺): m/z 498.

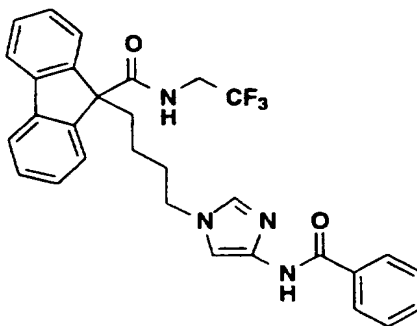
Anal. Calc. for C₂₉H₄₀NO₄P • 0.90 H₂O:

10 C, 67.78; H, 8.20; N, 2.73

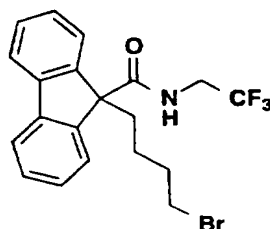
Found: C, 67.75; H, 7.91; N, 2.76.

Example 273

9-[4-[4-(Benzoylamino)-1H-imidazol-1-yl]butyl]-N-
15 (2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

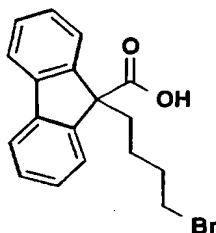


A.



20

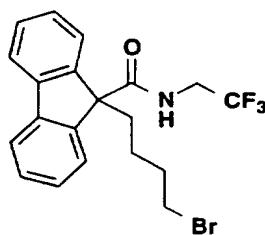
A(1).



To a solution of 9-fluorenenecarboxylic acid
5 (50 g, 240 mmol) in THF (1200 mL) at 0°C was added
dropwise a solution of n-butyllithium (2.5M, 211
mL, 530 mmol) in THF. The yellow reaction was
stirred at 0°C for 1 h, then 1,4-dibromobutane
(31.3 mL, 260 mmol) was added dropwise over 30
10 min. The reaction was stirred at 0°C for 30 min,
then the reaction was warmed to RT for 30 h. The
reaction was extracted with water (3 x 750 mL).
The combined aqueous layers were extracted with
ethyl ether (800 mL). The aqueous layer was made
15 acidic with HCl solution (1N, 500 mL), then
extracted with dichloromethane (3 x 750 mL). The
combined organic layers were dried over MgSO₄.
Evaporation gave title compound (71 g, 85%) as a
white solid.

20

A(2).

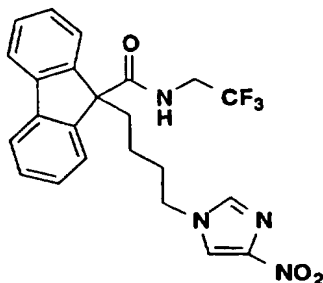


To a solution of Part A(1) acid (60 g, 173
25 mmol) and DMF (100 µL) in CH₂Cl₂ (600 mL) under
argon at 0°C was added oxalyl chloride (104 mL,
2.0M in CH₂Cl₂, 208 mmol) dropwise. The reaction
was stirred at 0°C for 10 min, then warmed to room
temperature and stirred for 1.5 h. The reaction

was concentrated in vacuo to give the crude acid chloride as a yellow oil. To a suspension of 2,2,2-trifluoroethylamine hydrochloride (25.9 g, 191 mmol) in CH₂Cl₂ (500 mL) at 0°C under argon was added triethylamine (73 mL, 521 mmol) followed by dropwise addition of a solution of the crude acid chloride in CH₂Cl₂ (15 mL). The reaction was stirred at 0°C for 1 h, diluted with CH₂Cl₂ (500 mL), and washed with water (2 x 300 mL), 1N HCl (2 x 300 mL), saturated NaHCO₃ (2 x 300 mL), and brine (2 x 300 mL), then dried over MgSO₄. Evaporation gave 80 g of a oil which was purified by flash chromatography on silica gel (2.5 kg). The crude product was loaded in a mixture of CH₂Cl₂ and hexane, and eluted with a step gradient of 10% EtOAc/hexane (4L) to 15% EtOAc/hexane (2L) to 20% EtOAc/hexane (4L). Pure fractions were combined and evaporated to give title compound (52.5 g, 71%) as a white solid (mp 88-92°C).

20

B.



A mixture of Part A (1.55 g, 3.64 mmol), 4-nitroimidazole (452 mg, 4.00 mmol), and anhydrous potassium carbonate (552 mg, 4.00 mmol) in DMF (5 mL) was heated at 50°C under argon for 6 h, cooled to RT, and the solvent was removed in vacuo. The yellow residue was partitioned between EtOAc (50 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (3 mL). The combined organic extracts were washed with water (3 x 10 mL) and

30

brine (20 mL), then dried over Na₂SO₄. Evaporation gave 1.77 g of a foamy gum, which was purified by flash chromatography on silica gel (120 g) eluting with 15% EtOAc/CH₂CH₂ to provide title compound

5 (1.51 g, 91%) as a white foam.

C. 9-[4-[4-(Benzoylamino)-1H-imidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

10 Palladium on carbon (10%) (35 mg, 0.033 mmol) was added to a solution of Part B compound (300 mg, 0.655 mmol) in dry EtOAc (2 mL), and the mixture was hydrogenated (balloon) at RT overnight. The reaction was degassed with argon, cooled to
15 0°C, and benzoyl chloride (83 µL, 0.72 mmol) was added dropwise. The reaction was stirred at 0 °C for 20 min, filtered through Celite, and washed with EtOAc (5 mL). The brown filtrate was washed with saturated NaHCO₃ (2 x 2 mL) and brine (1 mL),
20 then dried over Na₂SO₄. Evaporation gave 282 mg of a dark brown oil, which was purified by flash chromatography on silica gel (50 g) eluting with 2% MeOH/CH₂CH₂ to provide title compound (253 mg, 73%) as a brown foam.

25

MS (ES): 533 [M+H]

Anal. Calcd. for C₃₀H₂₇F₃N₄O₂ • 0.5 H₂O:

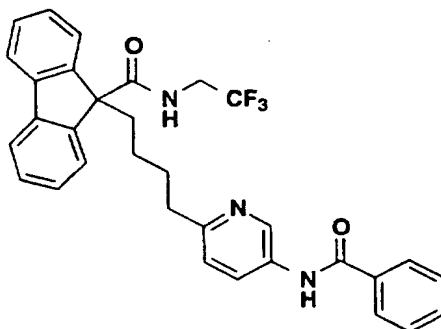
C, 66.53; H, 5.21; N, 10.35; F, 10.52

Found: C, 66.60; H, 5.13; N, 10.19; F, 10.86.

30

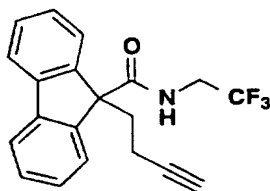
Example 274

9-[4-[5-(Benzoylamino)-2-pyridinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



5

A.

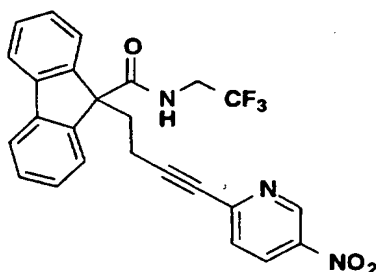


10 Butyllithium (12.6 mL, 31.5 mmol) was added dropwise over 5 min to a solution of 9-fluorene-carboxylic acid (3.0 g, 14.3 mmol) in THF (150 mL) at 0°C under argon. The reaction went cloudy during addition, then cleared upon
15 completion. The reaction was stirred at 0°C for 30 min, then 3-butynyl p-toluenesulfonate (9.6 g, 42.9 mmol) was added dropwise. The amber reaction was warmed to RT, then stirred for 24 h. The reaction solution was extracted with water (2 x 75 mL). The
20 combined aqueous layers were washed with Et₂O (50 mL), then acidified with 1N HCl (30 mL). The cloudy mixture was extracted with CH₂Cl₂ (2 x 50 mL), and the combined organic layers were dried over MgSO₄. Evaporation gave 1.85 g of a crude
25 orange gummy solid.

A portion (1.75 g) of crude acid product was dissolved in CH₂Cl₂ (20 mL) under argon. A catalytic amount of DMF (26 µL, 0.33 mmol) was

added, followed by oxalyl chloride (5.0 mL, 2.0 M in CH₂Cl₂, 10 mmol) slowly. After bubbling for a few minutes, the reaction was stirred at RT for 1.5 h, then concentrated in vacuo. The crude acid chloride was dissolved in CH₂Cl₂ (20 mL) and added dropwise to a suspension of 2,2,2-trifluoroethylamine hydrochloride (1.08 g, 8.02 mmol) and triethylamine (2.8 mL, 20 mmol) in CH₂Cl₂ (30 mL) at 0°C under argon. The reaction was stirred at 0°C for 10 min, diluted with CH₂Cl₂ (50 mL), washed with 1N HCl (2 x 20 mL) and saturated NaHCO₃ (20 mL), then dried over Na₂SO₄. Evaporation gave 2.24 g of a dark orange semi-solid, which was dissolved in 2:1 CH₂Cl₂:10% EtOAc/hexane and purified by flash chromatography on silica gel (175 g) eluting with 10% EtOAc/hexane to provide title compound (1.16 g, 22%) as a yellow solid (mp 109-113°C).

B.



20

Copper (I) iodide (4 mg, 0.02 mmol) was added to a solution of Part A compound (343 mg, 1 mmol) and 2-bromo-5-nitropyridine (203 mg, 1 mmol) in a mixture of triethylamine (3 mL) and DMF (2 mL). The yellow solution was degassed with argon then cooled to 0°C. Bis(triphenylphosphine)-palladium (II) chloride (14 mg, 0.02 mmol) was added and the reaction was stirred at 0°C for 10 min then at RT for 6 h. The reaction was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with

water (3 x 10 mL) then dried over K_2CO_3 .

Evaporation gave 520 mg of a brown foamy gum, which was purified by flash chromatography on silica gel (65 g) eluting with 20% EtOAc/hexane to provide
5 title compound (342 mg, 74%) as a yellow foam.

C. 9-[4-[5-(Benzoylamino)-2-pyridinyl]-
butyl]-N-(2,2,2-trifluoroethyl)-9H-
fluorene-9-carboxamide

10 A mixture of Part B compound (334 mg, 0.718 mmol) and 10% palladium on carbon (38 mg, 0.036 mmol) in EtOAc (2 mL) was hydrogenated (balloon) at RT for 6 h, filtered through Celite with the aid of EtOAc (30 mL), then concentrated in vacuo to give
15 292 mg of the aminopyridine as a brown gum.

A portion of amine (262 mg, 0.597 mmol) was dissolved in CH_2Cl_2 (3 mL), cooled to 0°C under argon, then treated sequentially with triethylamine (125 μ L, 0.896 mmol) and benzoyl chloride (77 μ L, 0.658 mmol) dropwise. The reaction was stirred at 0°C for 1 h, diluted with CH_2Cl_2 (5 mL), washed with saturated $NaHCO_3$ (2 x 1 mL) and brine (1 mL), then dried over Na_2SO_4 . Evaporation gave 360 mg of a green foam, which was purified by flash chromatography on silica gel (50 g) eluting with 50%
20 EtOAc/hexane to give 192 mg of impure product as a yellow glassy foam. The product was further purified by recrystallization from EtOAc/hexane. The first two crops were combined and dried in a
25 vacuum oven at 50°C overnight to afford title
30 compound (90 mg, 21%) as an off-white solid.

mp 166-169°C.

MS (ES): 544 [M+H].

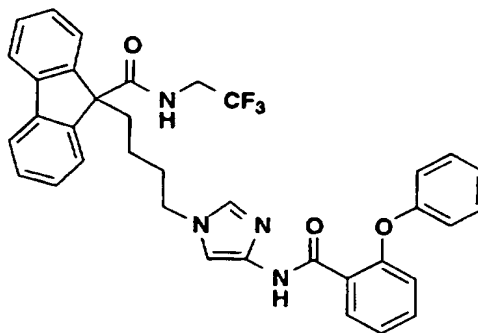
35 Anal. Calcd. for $C_{32}H_{28}F_3N_3O_2 \cdot 0.3 H_2O$:

C, 70.01; H, 5.25; N, 7.65

Found: C, 70.06; H, 4.98; N, 7.33.

Example 275

9-[4-[4-[(2-Phenoxybenzoyl)amino]-1H-imidazol-1-yl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



10 A. 2-Phenoxybenzoic Acid Chloride

To a solution of 2-phenoxybenzoic acid (500 mg, 2.33 mmol) and DMF (1 drop) in CH₂Cl₂ (10 mL) under argon was added oxalyl chloride (1.3 mL, 2.0M in CH₂Cl₂, 2.6 mmol) dropwise. Bubbling of escaping gasses continued for 5 min after addition. The reaction was stirred at room temperature for 1 h, then concentrated in vacuo to give the title compound as a crude pale yellow oil.

20 B. 9-[4-[4-[(2-Phenoxybenzoyl)amino]-1H-imidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

Palladium on carbon (10%) (74 mg, 0.07 mmol) was added to a solution of Example 273 Part B compound (640 mg, 1.4 mmol) in dry EtOAc (5 mL), and the mixture was hydrogenated (balloon) at RT overnight. The reaction was degassed with argon, cooled to 0°C, and triethylamine (290 µL, 2.10 mmol) was added. A solution of Part A acid chloride in CH₂Cl₂ (2 mL) was added dropwise over 5 min. The resulting thick reaction was stirred at

0°C for 30 min and filtered through Celite. The filter cake was rinsed with CH₂Cl₂ (3 x 20 mL).

The filtrate was washed with saturated NaHCO₃ (10 mL) and brine (10 mL), then dried over MgSO₄.

- 5 Evaporation gave 1.0 g of a dark brown foam, which was purified by flash chromatography on silica gel (75 g) eluting with 2% MeOH/CH₂Cl₂ to provide title compound (670 mg, 77%) as a yellow foam.

10 MS (ES): 625 [M+H].

Anal. Calcd. for C₃₆H₃₁F₃N₄O₃:

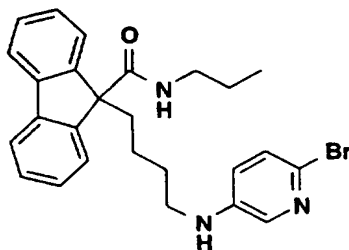
C, 69.22; H, 5.00; N, 8.97; F, 9.12

Found: C, 68.84; H, 4.90; N, 8.80; F, 8.80.

15

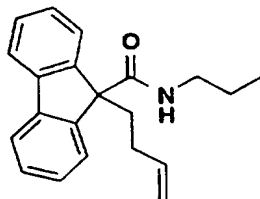
Example 276

9-[4-[(2-Bromo-5-pyridinyl)amino]butyl]-N-propyl-9H-fluorene-9-carboxamide



20

A.



- 25 The title compound was prepared from 9-fluorenenecarboxylic acid (4.2g, 20 mmol) and 4-bromo-1-butene (2.2 mL, 22 mmol) according to the procedure for Part A compound in Example 274 to give title compound (5.1 g, 84%) as a white solid (mp 67-69°C).

B. 9-[4-[(2-Bromo-5-pyridinyl)amino]-
butyl]-N-propyl-9H-fluorene-9-carboxamide

A solution of Part A compound (500 mg, 1.64
5 mmol) in THF (2 mL) was added to a solution of 9-
borabicyclo[3.3.1]nonane (3.3 mL, 0.5M in THF, 1.64
mmol) at 0°C under argon. The clear, colorless
reaction was stirred at RT for 5 h, then diluted
further with dioxane (10 mL). Anhydrous potassium
10 phosphate anhydrous (316 mg, 1.49 mmol) was added,
followed by tetrakis(triphenylphosphine)palladium
(52 mg, 0.045 mmol). 2-Bromo-5-nitropyridine (302
mg, 1.49 mmol) was added and the reaction was
stirred at 60°C overnight, then cooled to RT.
15 Water (30 mL) was added and the reaction was
stirred vigorously in the air for 2 h. The
reaction mixture was extracted with EtOAc (100 mL,
then 20 mL), and the combined organic layers were
washed with brine (2 x 20 mL), then dried over
20 MgSO₄. Evaporation gave 1.2 g of a brown oil,
which was dissolved in a minimum amount of CH₂Cl₂
and purified by flash chromatography on silica gel
(75 g) eluting with 40% EtOAc/hexane to provide 200
mg of impure product as a yellow foam. Additional
25 chromatography eluting with 50% EtOAc/hexane gave
title compound (147 mg, 19%) as a yellow solid.

mp 139-141°C.

MS (ES): 478/480 [M+H].

30 Anal. Calcd. for C₂₆H₂₈BrN₃O • 0.3 H₂O:

C, 64.54; H, 5.96; N, 8.68

Found: C, 64.61; H, 5.88; N, 8.66.

Examples 277 to 286

35

The following additional compounds were
prepared following procedures set out hereinbefore.

Example 277

9-[2-[[[4-(Benzoylamino)phenyl]sulfonyl]amino]ethyl]-
N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

5

mp 235-236°C

MS (ES) 594 (M+H); 1187 (2M+H)

Anal. Calc'd for C₃₁H₂₆F₃N₃O₄S:

C, 62.72; H, 4.41; N, 7.08; F, 9.60; S,

10 5.40

Found: C, 62.56; H, 4.45; N, 7.00; F, 9.54; S,
5.21.

Example 278

15

9-(4-Phenylbutyl)-N-propyl-9H-fluorene-9-carboxamide

mp 88-90°C

MS (CI) 384 (M+H)

20 Anal. Calc'd for C₂₇H₂₉NO:

C, 84.56; H, 7.62; N, 3.65

Found: C, 84.62; H, 7.66; N, 3.72.

Example 279

25

3-[(9-Propyl-9H-fluoren-9-yl)sulfonyl]propanoic acid,
methyl ester

mp 74-77°C

MS (FAB, + ions) m/z 376 (M+NH₄) m/z 359 (M+H)

30 Anal. Calc'd for C₂₀H₂₂O₄S•0.29 H₂O:

C, 66.04; H, 6.26; N, 8.81

Found: C, 66.04; H, 6.11; N, 8.45.

Example 280

9-[4-[(6-Ethoxy-2-benzothiazolyl)thio]butyl]-N-propyl-9H-fluorene-9-carboxamide

5 mp 109-111°C

MS (ES, + ions) m/z 517 (M+H)

Anal. Calc'd for C₃₀H₃₂N₂O₂S₂ + 0.40 mol H₂O:

C, 68.78; H, 6.31; N, 5.35; S, 12.24

Found: C, 68.56; H, 6.07; N, 5.57; S, 12.23.

10

Example 281

9-[3-[(6-Ethoxy-2-benzothiazolyl)thio]propyl]-N-propyl-9H-fluorene-9-carboxamide

15 mp 82-85°C

MS (ES, + ions) m/z 503 (M+H)

Anal. Calc'd for C₂₉H₃₀N₂O₂S₂ + 0.56 mol H₂O:

C, 67.93; H, 6.12; N, 5.46; S, 12.50

Found: C, 68.03; H, 5.83; N, 5.36; S, 12.51.

20

Example 282

(Z)-9-[4-(Diethoxyphosphinyl)-2-butenyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

25

mp 88-91°C

MS (CI-NH₃, + ions) m/z 482 (M+H)

Anal. Calc'd for C₂₄H₂₇NO₄PF₃:

C, 59.87; H, 5.65; N, 2.91; P, 6.43; F,

30 11.84

Found: C, 59.52; H, 5.61; N, 2.89; P, 6.92; F, 11.94.

Example 283

9-[4-(Diethoxyphosphinyl)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

5

mp 87-89°C

MS (FAB) m/z 484 (M+H)

Anal. Calc'd for C₂₄H₂₉NO₄PF₃ + 0.13 mol H₂O:

C, 59.33; H, 6.07; N, 2.88; P, 6.37; F,

10 11.73

Found: C, 59.09; H, 5.98; N, 2.95; P, 6.51; F,

11.92.

Example 284

15

9-[4-(Dibutoxyphosphinyl)butyl]-N-(2,2,3,3,3-pentafluoropropyl)-9H-fluorene-9-carboxamide

mp 56-57°C

20 MS (ES, + ions) m/z 590 (M+H)

Anal. Calc'd for C₂₉H₃₇NO₄F₅P:

C, 59.08; H, 6.33; N, 2.38; P, 5.25; F,

16.11

Found: C, 58.80; H, 6.34; N, 2.26; P, 5.05; F,

25 15.90.

Example 285

9-[4-(Dibutoxyphosphinyl)butyl]-N-propyl-9H-xanthene-9-carboxamide

30

mp 64-67°C

MS (ES, + ions) m/z 516 (M+H)

Anal. Calc'd for C₂₉H₄₂O₅NP:

C, 67.55; H, 8.21; N, 2.72; P, 6.01

35 Found: C, 67.25; H, 8.17; N, 2.68; P, 5.99.

Example 286

9-[4-(Dibutoxyphosphinyl)butyl]-N-(2,2,3,3,4,4,4-heptafluorobutyl)-9H-fluorene-9-carboxamide

5 MS (ES, + ions) m/z 657 (M+NH₄), 640 (M+H)

Anal. Calc'd for C₃₀H₃₇NF₇PO₄:

C, 56.34; H, 5.83; N, 2.19; F, 20.79; P,
4.84

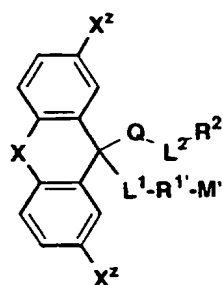
Found: C, 56.03; H, 5.91; N, 2.15; F, 20.74; P,

10 4.77.

The following compounds of the invention
may be prepared following the procedures described
hereinbefore and in the working Examples.

15

TABLE



X is bond r O

X² is H or F

Q is CONH, CO or SO₂

L²-R² is CH₂CF₃, CH₂CF₂CF₃, propyl, butyl,

$$-(\text{CH}_2)_5\text{PO}(\text{Obutyl})_2$$

M' is benzamido, 2-phenoxybenzamido,

2-phenylbenzamido, cyclohexanecarboxamido

2-methoxy-3-pyridinecarboxamido,

benzenesulfonamido, phenylureido,

t-butoxycarbonylamino,

2,3-dihydro-1-oxo-1H-isoindol-2-yl,

2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl (2-phthalimido)

INCLUDES: N-OXIDES OF ALL PYRIDINES

Examples of $-L^1-R^1-$

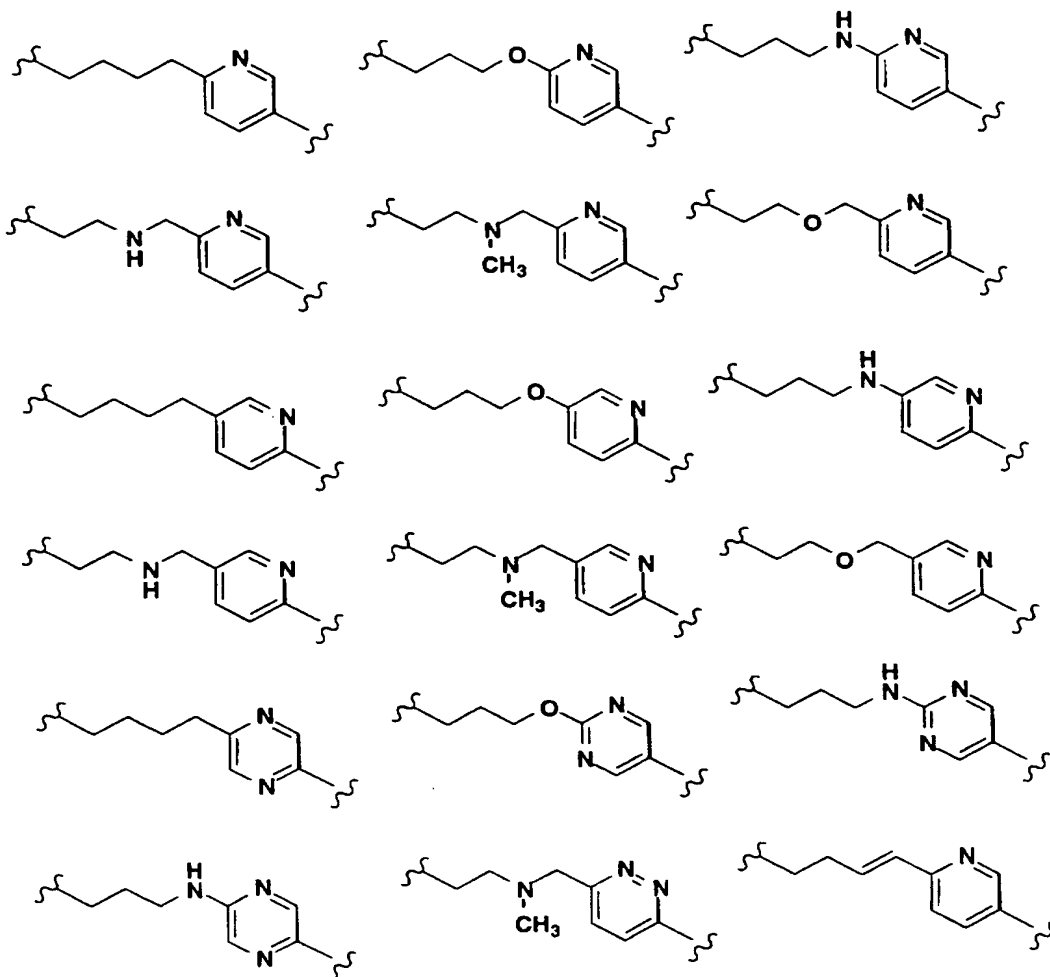


TABLE (continued)

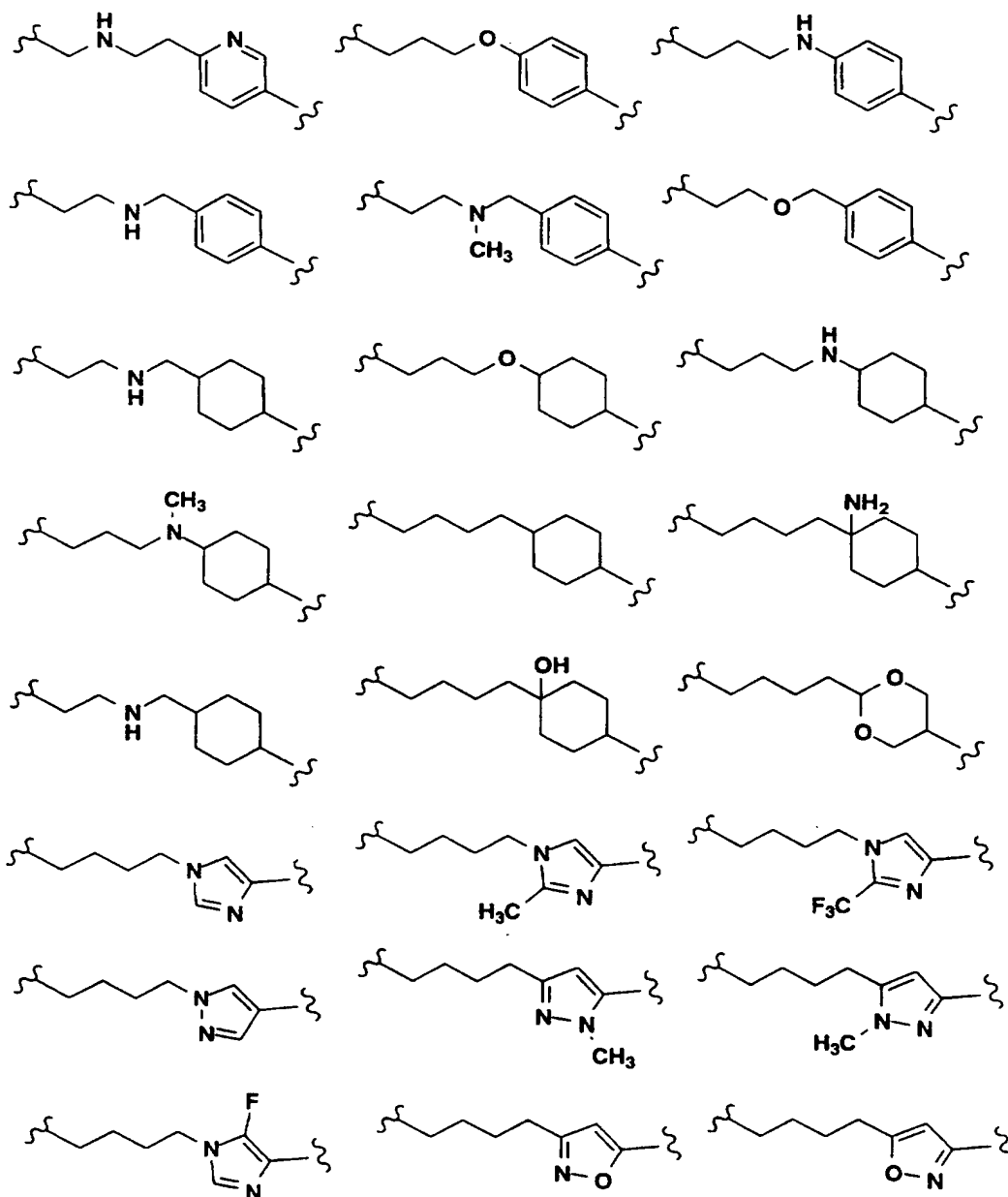
Examples of $-L^1-R^1-$ 

TABLE (c ntinued)

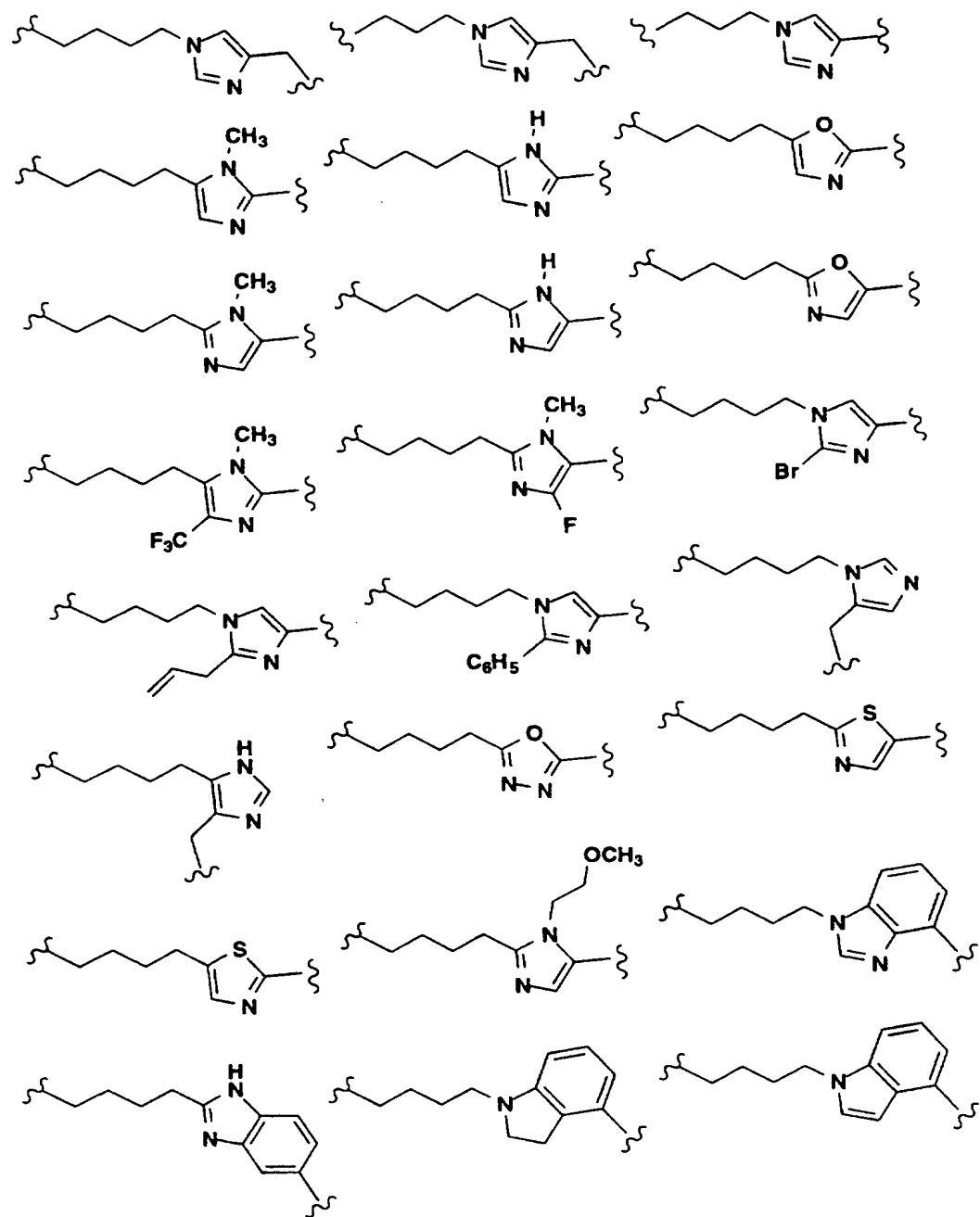
Examp l s of -L¹-R^{1'}-

TABLE (c ntinu d)

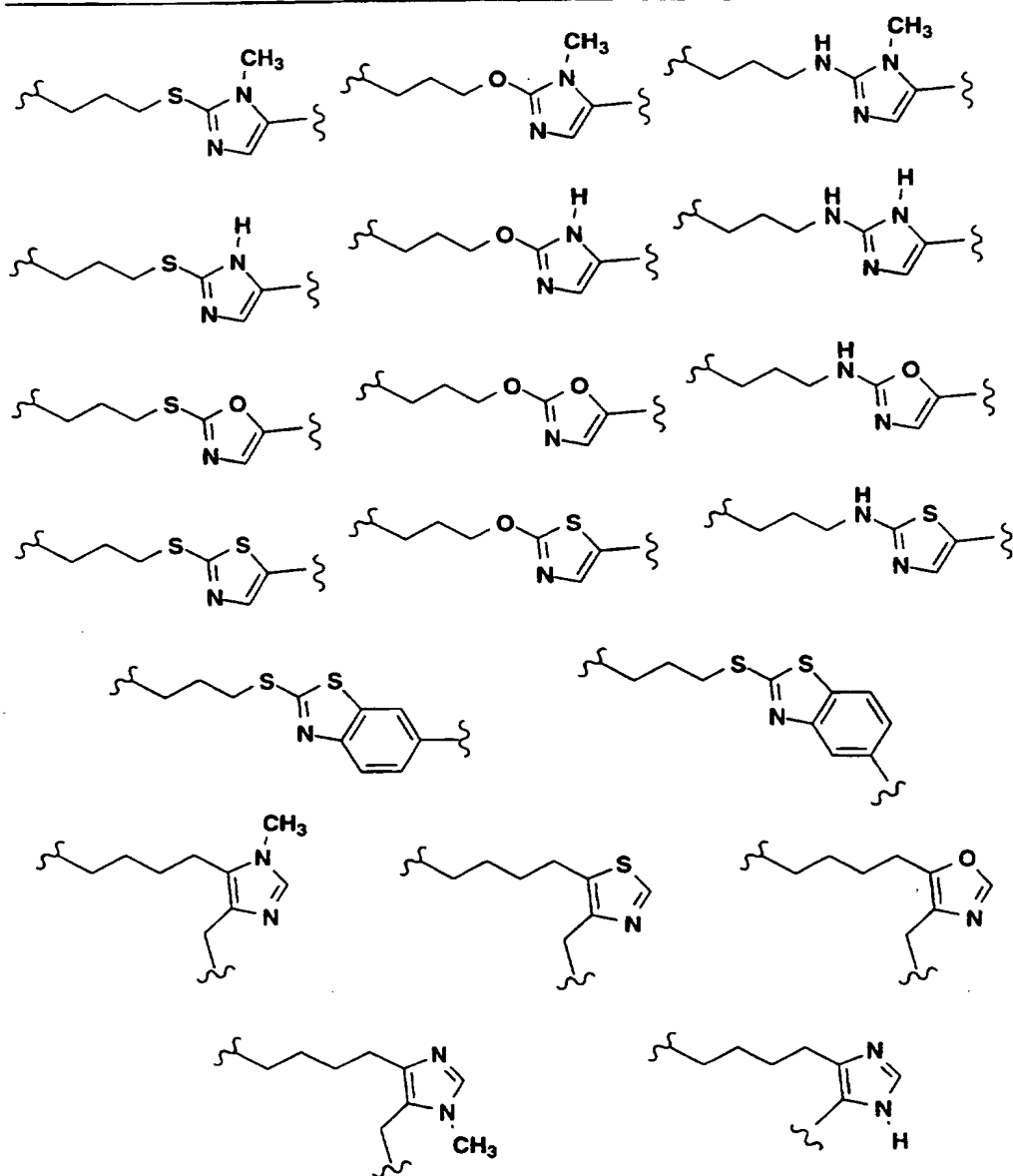
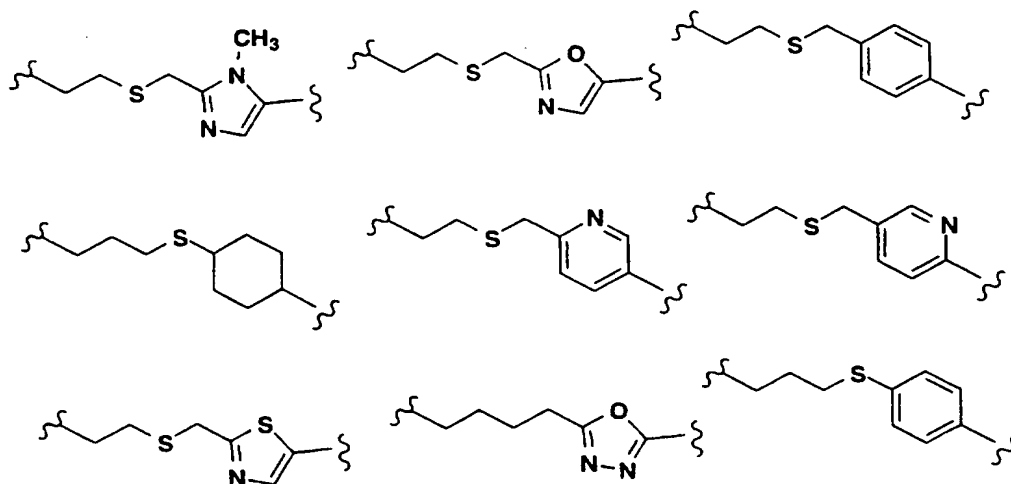
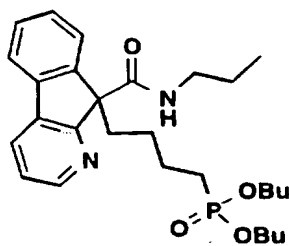
Examp l s of -L¹-R^{1'}-

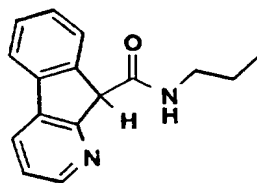
TABLE (continued)

Examp^ls of -L¹-R^{1'}-Example 287

9-[4-(Dibutoxyphosphinyl)butyl]-N-propyl-9H-indeno-
 5 [2,1-b]pyridine-9-carboxamide



A.



10

A THF (5 ml) solution of 1-aza-fluorene
 (233 mg, 1.39 mmol; prepared from benzo(f)quinoline
 by known procedures, Kloc, K. Journal f. prakt.
 15 Chemie, 319, 959-967 (1977) and Kloc, K.
 Heterocycles, 9, 849-852 (1978)) and n-

propylisocyanate (0.13 ml, 1.39 mmol) was degassed three times by cooling to -78°C, evacuating, and allowing to warm to room temperature, and finally purging with argon. To the degassed solution at
5 -10°C was added dropwise sodium bis(tri-methylsilyl)amide (1.4 ml, 1 M in THF). After 5 min, a second portion of n-propylisocyanate (0.13 ml, 1.39 mmol) was added to the red solution. The now green colored reaction mixture was quenched
10 after a further 15 min with saturated NH₄Cl. The aqueous layer was extracted with EtOAc, the organics washed with brine, dried over Na₂SO₄ and evaporated in vacuo to give a red colored oily-solid residue (535 mg). The residue was purified
15 by flash column chromatography (SilicAR[®] buffered silica gel, 5 by 7 cm), eluting with 20% EtOAc:CH₂Cl₂, and flushing with 5% MeOH:CH₂Cl₂ to give title compound (202 mg, 58% yield) as an orange colored solid,
20
mp 131-133°C.
MS: (FAB, M+H⁺): m/z 253⁺.

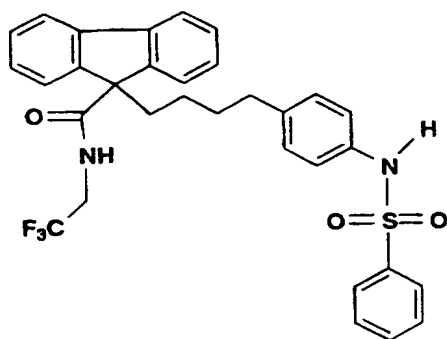
25 B. 9-[4-(Dibutoxyphosphinyl)butyl]-N-propyl-9H-indeno[2,1-b]pyridine-9-
carboxamide

To a THF (5 ml, degassed) suspension of Part A compound (250 mg, 0.990 mmol) at 0°C under argon was added dropwise n-BuLi (0.8 ml, 2.5 M in
30 hexanes), with a red colored solid falling from solution after all the base was added. After 10 min, Example 202 Part A iodide (403 mg, 1.07 mmol) was added and the reaction stirred 1 h. Little reaction had occurred by TLC analysis, so a second
35 portion of Example 202 Part A iodide (110 mg, 0.294 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. The brown

reaction mixture was quenched with sat. NH_4Cl and the aqueous layer was extracted twice with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4 , and concentrated to a brown colored oil (740 mg). The residue was purified by flash column chromatography (SilicAr CC-7, 74 g), eluting with 3.75% $\text{MeOH}:\text{CH}_2\text{Cl}_2:0.2\% \text{NH}_4\text{OH}$ to give impure title compound (386 mg). The residue was purified further by flash column chromatography (SilicAr CC-7, 60 g), eluting with 2.5% $\text{MeOH}:\text{EtOAc}$ to give title compound (260 mg, 52% yield) as a colored oil. MS (electrospray, + ions) m/z 501 ($\text{M}+\text{H}$).

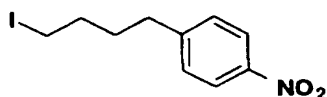
Example 288

9-[4-[4-[(Phenylsulfonyl)amino]phenyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



20

A.

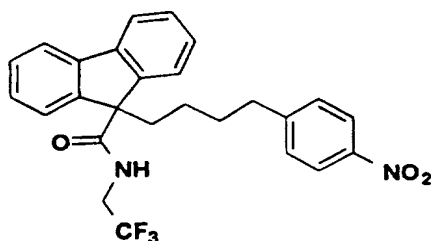


A solution of iodine (1.40 g, 5.5 mmol) in THF (5 mL) was added dropwise over 5 min to a solution of 4-(4-nitrophenyl)-1-butanol (975 mg, 5 mmol), triphenylphosphine (1.44 g, 5.5 mmol), and imidazole (749 mg, 11 mmol) in THF (10 mL) under argon at room temperature. The dark orange solution was stirred at room temperature for 15 min, diluted with hexane (50 mL), then washed with

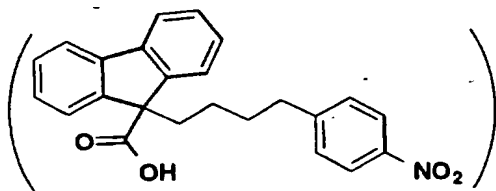
10% sodium bisulfite, saturated NaHCO_3 , and brine (20 mL each). The organic layer was dried over MgSO_4 and filtered. To the filtrate was added silica gel (4 g) and the mixture was concentrated in vacuo to give a yellow powder, which was purified by flash chromatography on silica gel (120 g) eluting with 25% CH_2Cl_2 /hexane to give title iodide (1.33 g, 87%) as a pale yellow crystalline solid (mp 44-45°C).

10

B.



Butyllithium (2.0 mL, 2.5M in hexane, 5.0 mmol) was added to a solution of 9-fluorene-carboxylic acid (480 mg, 2.3 mmol) in THF (10 mL) at 0°C under argon over 5 min. The reaction went from a clear solution to a white suspension then to a yellow solution during addition. The reaction was stirred at 0°C for 20 min, whereupon a solution of Part A iodide (671 mg, 2.2 mmol) in THF (4 mL) was added dropwise over 5 min. The reaction was stirred at 0 °C for 1.5 h, warmed to room temperature, then stirred at room temperature for 3.5 h. The reaction was quenched with 1N HCl to pH \approx 3, diluted with water (10 mL), then extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water and brine (10 mL each), then dried over MgSO_4 . Evaporation gave a residue, which was azeotroped with toluene (10 mL) to give crude acid in the form of a dark foam



To a solution of the crude acid prepared above containing 3 drops of DMF in CH₂Cl₂ (6 mL) at room temperature under argon was added oxalyl chloride (3 mL, 2.0M in CH₂Cl₂, 6.0 mmol). The reaction was allowed to stir at room temperature for 1.5 h. The reaction was concentrated in vacuo to provide a dark oil, which was diluted with THF (5 mL) and cooled to 0°C under argon.

Trifluoroethylamine (0.63 g, 8 mmol) was added dropwise over 2 min, and the reaction was stirred at 0°C for 3 h. The reaction was partitioned between EtOAc (30 mL) and water (10 mL). The organic layer was washed with 1N HCl (7 mL) and brine (5 mL), then dried over MgSO₄. Evaporation gave 974 mg of a brown oil, which was dissolved in CH₂Cl₂ and purified by flash chromatography on silica gel (75 g) eluting with 15:85 EtOAc/hexane to afford title compound (0.75 g, 69%) as a thick oil.

C. 9-[4-[4-[(Phenylsulfonyl)amino]phenyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A mixture of Part B compound (220 mg, 0.47 mmol) and 10% palladium on carbon (20 mg) in EtOAc (15 mL) was hydrogenated (balloon pressure) at room temperature for 18 h, filtered through Celite with the aid of EtOAc, then concentrated in vacuo to give a residue, which was pumped under high vacuum to provide a thick oil.

Phenylsulfonyl chloride (80 mg, 0.46 mmol) was added to a solution of the crude amine (≈ 0.45 mmol) and pyridine (35 mg, 0.46 mmol) in CH₂Cl₂ (4

mL) at room temperature under argon. The reaction was stirred for 2 h, diluted with ethyl acetate (50 mL), washed with 1N HCl (10 mL) and water (10 mL), then dried over MgSO₄. Evaporation gave an oil, which was adsorbed onto silica gel (10 g), then purified by flash chromatography on silica gel (50 g) eluting with 30% EtOAc/hexane to give 0.23 g (88%) of title compound as a pink solid.

mp: 130-132°C.

Anal Calc'd for C₃₂H₂₉N₂SO₃F₃ + 0.2 CH₂Cl₂:

C, 64.93; H, 4.98; N, 4.70; S, 5.38; F,

9.57

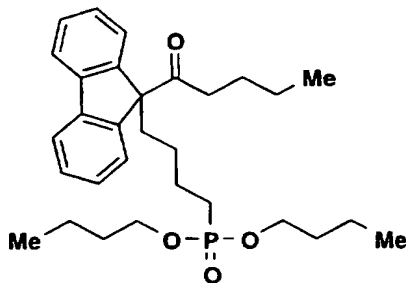
Found: C, 65.16; H, 5.08; N, 4.55; S, 5.52; F,

9.17.

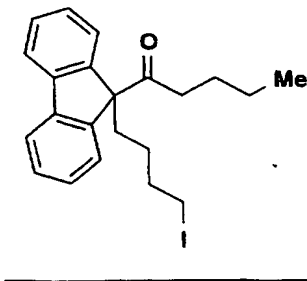
Example 289

[4-[9-(1-Oxopentyl)-9H-fluorene-9-yl]butyl]phosphonic acid, dibutyl ester

20

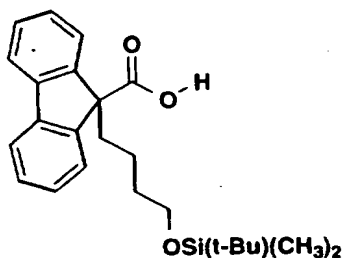


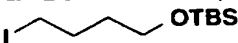
A.



25

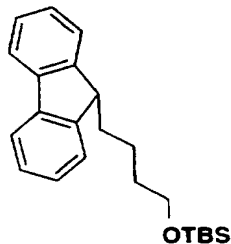
A(1).



To a solution of 5 g (23.78 mmol) of 9-fluorene-2-carboxylic acid in 20 mL of THF, under argon at 0°C, was added 20.6 mL (52.32 mmol) of n-butyl-lithium (2.5 M in hexanes) dropwise. The orange-red anion was stirred for 0.5 h, at which time 7.5 g (23.78 mmol) of  (where TBS is t-Bu(CH₃)₂•Si-) was added dropwise. The reaction gradually warmed to room temperature and was stirred for 36 h, at which time it was diluted with a 1:1 mixture of ethyl acetate/H₂O (250 mL). The organics were washed with NaHCO₃, brine, dried (Na₂SO₄) and evaporated. Flash chromatography was performed on 250 g of silica gel eluting with 9:1 dichloromethane/isopropanol to provide 4.9 g (52%) of title compound as a yellow oil.

TLC: Silica gel (9:1 dichloromethane/isopropanol)
R_f = 0.50.

A(2).



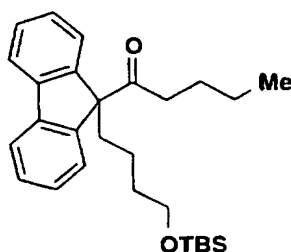
25

To 550 mg (1.38 mmol) of Part A(1) compound was added 5 mL of DMSO. The reaction was stirred for 18 h, under argon at room temperature, at which

time it was diluted with ether and washed with water (3x). Flash chromatography was performed on 100 g of silica gel eluting with 95:5 hexanes/ethyl acetate to provide 340 mg (70%) of title compound
5 as a pale yellow oil.

TLC: Silica gel (95:5 hexanes/ethylacetate)
 R_f = 0.31.

10 A(3).



To a solution of 340 mg (0.96 mmol) of Part A(2) compound in 3 mL of THF, under argon at 0°C,
15 was added dropwise 462 μ L (1.16 mmol) of n-butyllithium (2.5 M in hexanes). The resulting anion was stirred for 0.5 h, at which time 140 μ L (1.16 mmol) of freshly distilled valeryl chloride (Aldrich) was added dropwise. The reaction was
20 stirred for 2 h, at which time it was diluted with ether and quenched with NaHCO_3 . The organics were washed with water, brine, dried (NaSO_4) and evaporated. Flash chromatography was performed on 100 g of silica gel eluting with 95:5
25 hexanes/dichloromethane to provide 290 mg (69%) of title compound as a pale yellow oil.

TLC: Silica gel (95:5 hexanes/ethyl acetate)
 R_f = 0.36.

30 MS (CI- NH_3 , + ions) m/e 397 (M+H).

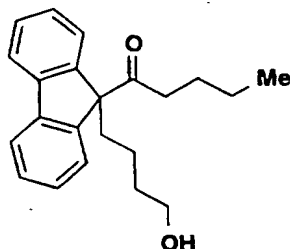
Anal. Calcd. for $C_{24}H_{32}O_3Si + 0.15 \text{ mol } H_2O$.

C, 72.20; H, 8.15

Found: C, 72.20; H, 7.88.

5

A(4).



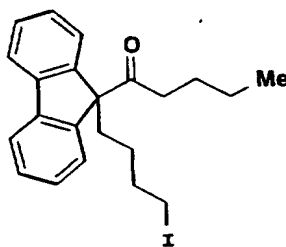
To 200 mg (0.46 mmol) of Part A(3) compound was added 1 mL of 5:95 aqueous HF/acetonitrile.

10 The reaction was stirred, under argon at room temperature, for 3 h, at which time it was diluted with ether and washed with $NaHCO_3$, water (3x), brine, dried ($MgSO_4$) and evaporated. Flash chromatography was performed on 50 g of silica gel
15 eluting with 7:3 hexanes/ethyl acetate to provide 120 mg (81%) of title compound as a pale yellow oil.

TLC: Silica gel (8:2 hexanes/ethyl acetate)

20 $R_f = 0.15$.

A(5).



25

To a solution of 120 mg (0.37 mmol) of Part A(4) compound in 1.5 mL of THF, under argon at $0^\circ C$, was added 55 mg (0.81 mmol) of imidazole followed by 126 mg (0.48 mmol) of triphenylphosphine. The

mixture was stirred for 0.5 h, at which time 122 mg (0.48 mmol) of iodine in 1 mL of THF was added dropwise. The reaction was stirred for 1 h at 0°C, 1 h at room temperature, then diluted with hexanes and washed with fresh sodium bisulfite solution, NaHCO₃, water, brine, dried (MgSO₄) and evaporated. Flash chromatography was performed on 25 g of silica gel eluting with 9:1 hexanes/ethyl acetate to provide 130 mg (81%) of title compound as a colorless oil.

TLC: Silica gel (9:1 hexanes/ethyl acetate)
R_f = 0.40.

15 B. [4-[9-(1-Oxopentyl)-9H-fluorene-9-yl]butyl]phosphonic acid, dibutyl ester

To 220 mg (0.51 mmol) of Part A iodide was added 688 µL (2.55 mmol) of tributylphosphite (neat). The mixture was heated to 120°C for 32 h and bulb to bulb distilled (5 mm, 100°C) to remove lower boiling impurities and provide 260 mg (87%) of title compound as a pale yellow oil.

MS (ES NH₃, + ions) m/e 516 (M+NH₄), 499 (M+H).

25

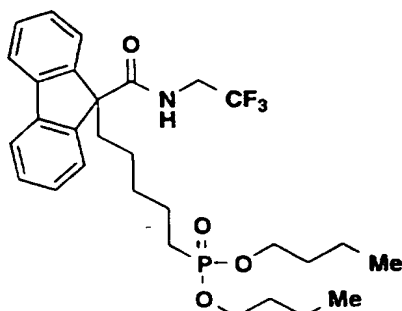
Anal. Calcd for C₃₀H₄₃O₄P + 0.24 mol CH₂Cl₂.

C, 69.98; H, 8.44; P, 5.97

Found: C, 69.97; H, 8.41; P, 6.26.

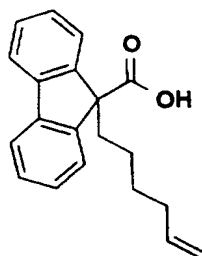
Example 290

9-[5-(Dibutoxyphosphinyl)pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



5

A.



10 To a solution of 3.0 g (14.30 mmol) of 9-fluorenecarboxylic acid in 50 mL of THF, under argon at 0°C, was added dropwise 11.4 mL (28.60 mmol) of n-BuLi (2.5 M in hexanes). The anion was stirred for 0.5 h at which time 2.3 mL (17.16 mmol)

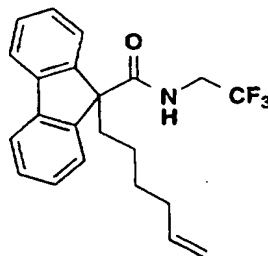
15 of 6-bromo-1-hexene was added dropwise. The reaction gradually warmed to room temperature and was stirred for 18 h, at which time it was diluted with a 1:1 mixture of ethyl acetate/water (200 mL). The organics were washed with NaHCO₃, water, brine,

20 dried (Na₂SO₄) and evaporated. Flash chromatography was performed on 200 g of silica gel eluting with 95:5 dichloro-methane/isopropanol to provide 900 mg (22%) of title compound as a pale yellow solid.

25

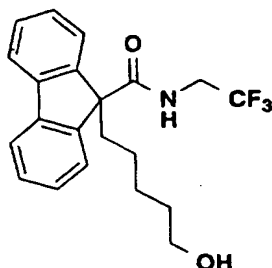
MS (CI-NH₃, + ions) m/z 310 (M + NH₄), 293 (M + H).

B.



- To a solution of 800 mg (2.74 mmol) of Part A compound in 10 mL of CH_2Cl_2 , under argon at room temperature, was added dropwise two drops of DMF and 2.0 mL (4.11 mmol) of oxalyl chloride (2.0 M in CH_2Cl_2). The reaction was stirred for 45 min. when it was evaporated to dryness.
- In another flask, 446 mg (3.29 mmol) of 2,2,2-trifluoroethylamine in 10 mL of CH_2Cl_2 , under argon at 0°C , was added 1.1 mL (8.22 mmol) of triethylamine. This slurry was stirred for 15 min at which time the above acid chloride, in 5 mL of CH_2Cl_2 , was added dropwise. The reaction gradually warmed to room temperature and was stirred for 18 h, at which time it was diluted with ether and washed with water, 1N HCl, NaHCO_3 , water, brine, dried (Na_2SO_4) and evaporated. Flash chromatography was performed on 100 g of silica gel eluting with 6:4 hexanes/ethyl acetate to provide 740 mg (74%) of title compound as a pale yellow solid.
- MS (ES NH_3 , - ions) m/z 372 ($M - H$).

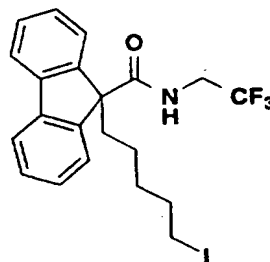
C.



250 mg (0.67 mmol) of Part B compound in 2
5 mL of methanol, at -78°C , was treated with a stream
of O_2/O_3 for 0.5 h, at which time the reaction was
purged with N_2 and treated with 76 mg (2.0 mmol) of
sodium borohydride pellets. The reaction gradually
warmed to room temperature and was stirred for 18
10 h, at which time it was diluted with ether and
washed with NH_4Cl , water, brine, dried (Na_2SO_4) and
evaporated. Flash chromatography was performed on
100 g of silica gel eluting with 3:2 hexanes/ethyl
acetate to provide 200 mg (79%) of title compound
15 as a white solid.

MS (ES NH_3 , - ions) m/z 376 ($\text{M} - \text{H}$).

D.



20

To a solution of 200 mg (0.53 mmol) of Part
C compound in 3 mL of THF, under argon at 0°C , was
added 76 mg (1.12 mmol) of imidazole followed by
25 180 mg (0.69 mmol) of triphenylphosphine. This
mixture was stirred for 0.5 h at which time 175 mg
(0.69 mmol) of iodine in 3 mL of THF was added
dropwise. The reaction was stirred at 0°C for 1 h,

at room temperature for 1 h, then diluted with hexanes and washed with fresh sodium bisulfite solution. The organics were washed with NaHCO_3 , water, brine, dried (Na_2SO_4) and evaporated. Flash chromatography was performed on 50 g of silica gel eluting with 9:1 hexanes/ethyl acetate to provide 200 mg (78%) of title compound as a white solid.

10 E. 9-[5-(Dibutoxyphosphinyl)pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

To 200 mg (0.41 mmol) of Part D compound was added 555 μL (2.05 mmol) of tributylphosphite (neat). The mixture was heated to 120°C for 18 h and bulb to bulb distilled (5 mm, 100°C) to remove lower boiling impurities and provide 234 mg (98%) of title compound as a white solid.

mp $88-91^\circ\text{C}$.

20 MS (ES NH_3 , + ions) m/z 571 ($\text{M}+\text{NH}_4$), 554 ($\text{M}+\text{H}$).

Anal. Calcd. for $\text{C}_{29}\text{H}_{39}\text{NO}_4\text{PF}_3 + 0.3 \text{ H}_2\text{O}$:

C, 62.31; H, 7.14; N, 2.51; P, 5.54

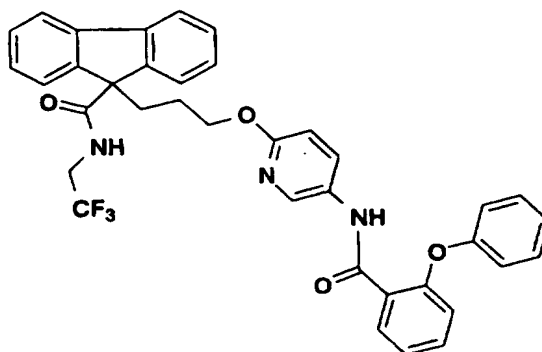
Found: C, 62.35; H, 7.21; N, 2.38; P, 5.76.

25

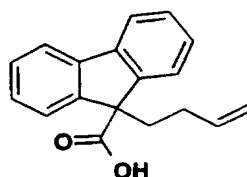
Example 291

9-[3-[[5-[(2-Phenoxybenzoyl)amino]-2-pyridinyl]-oxy]-propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

5



A.

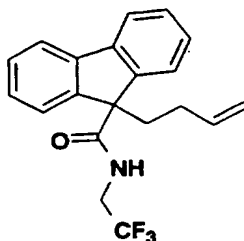


10

To a stirred solution of 12.6 g (60 mmol) of 9-fluorenicarboxylic acid in 600 mL of dry THF at 0° under argon was added, over 20 min, 53 mL of 2.5 M n-butyllithium in hexane (132.5 mmol). The mixture was stirred for 30 min and then 7.3 mL (72 mmol) of 4-bromo-1-butene were added. The reaction was stirred at 0°C for 10 min and then at room temperature for 2 days. Additional 4-bromo-1-butene (3.0 mL, 30 mmol) was added and stirring was continued for 2 days longer. Water (100 mL) was added and the mixture was concentrated to remove THF. Additional water was added and the mixture was extracted with ether (2 x 200 mL). The aqueous layer was layered with CH₂Cl₂ and acidified with 1N HCl (pH <2). After three extractions with CH₂Cl₂, the combined CH₂Cl₂ fraction was washed with water (2x), dried (MgSO₄), and concentrated to give 14.5

g (92%) of title compound as an amorphous pale yellow solid.

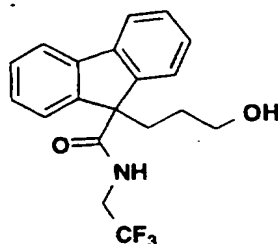
B.



5

Part A compound (9.1 g, 34.5 mmol) was dried by concentration *in vacuo* from dry THF and dry toluene (2x) and then *in vacuo* overnight. To a solution of this acid in 100 mL of dry CH₂Cl₂ and 133 μL of DMF under nitrogen was slowly added 26 mL of 2.0 M oxalyl chloride in CH₂Cl₂ (52 mmol). The reaction was stirred at room temperature for 1.5 h and then concentrated *in vacuo* and dried for 1 h at 0.5 mm to give the crude acid chloride of Part A compound. Triethylamine (14.5 mL, 104 mmol) was added to a stirred suspension of 2,2,2-trifluoro-ethylamine hydrochloride in 70 mL of dry CH₂Cl₂ at 0°C under argon and the slurry was stirred at 0°C for 10 min. A solution of the crude acid chloride of Part A compound in 35 mL of CH₂Cl₂ was added over 15 min keeping the internal temperature < 12°C. The reaction was stirred at 0°C for 1 h and then it was diluted with 175 mL of CH₂Cl₂. The CH₂Cl₂ was washed with 1N HCl (2x70 mL), water (175 mL), 5% NaHCO₃ (110 mL) and water (2x175 mL), dried (Na₂SO₄), and concentrated to give crude title compound as a solid (11.4 g). This solid was combined with an additional 6.54 g of crude title compound, and the combined crude title compound was chromatographed over 700 g of silica gel using CH₂Cl₂ to provide 15.5 g (82%) of title compound as a solid having mp 105-107°C.

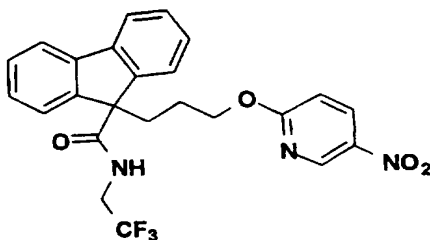
C.



- 5 A solution of Part B compound (0.50 g, 1.44 mmol) in 20 mL of 1:1 dichloromethane/methanol at -78°C was treated with a stream of O₂/O₃ until the solution turned light blue. The mixture was treated with NaBH₄ (1 pellet, 0.2 g, 5.26 mmol) and stirred
- 10 for 18 h. The resulting colorless solution was diluted with 1:1 NH₄Cl solution/ethyl acetate (150 mL) and the layers separated. The organic fraction was dried (MgSO₄), filtered, and concentrated to give 0.44 g (89%) of title compound as a white
- 15 solid.

mp 111-114°C.

D.



20

- A solution of Part C compound (0.50 g, 1.43 mmol) in THF (7 mL) was treated with NaH (38 mg, 1.57 mmol) and stirred for 0.5 h. After all of the
- 25 gray solid was consumed, 2-bromo-5-nitropyridine (0.32 g, 1.57 mmol) was added to the reaction mixture. The resulting dark orange solution was stirred at room temperature for 18 h, diluted with 1:1 water/ethyl acetate (150 mL) and the layers

separated. The organic fraction was dried (MgSO₄), filtered, and concentrated. The remainder was purified by flash chromatography on silica gel (50 g) eluting with 1:4 ethyl acetate/hexane to give
5 title compound (0.81 g, 99%) as a pale yellow yellow oil.

E. 9-[3-[[5-[(2-Phenoxybenzoyl)amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,
10 monohydrochloride

A mixture of Part D compound (0.78 g, 1.65 mmol) and 10% palladium on carbon (80 mg) in EtOAc (20 mL) was hydrogenated (balloon pressure) at room
15 temperature for 18 h. 2-Phenoxybenzoyl chloride (0.46 g, 2.00 mmol) was added to the solution of the crude amine (\approx 1.65 mmol) and pyridine (0.14 g, 1.78 mmol). The reaction was stirred for 2 h, diluted with ethyl acetate (50 mL), washed with
20 NaHCO₃ solution (20 mL), and dried over MgSO₄. Evaporation gave an oil, which was purified by flash chromatography on silica gel (75 g) eluting with 40% EtOAc/hexane to give 0.78 g (75%) of a white foam. The foam was diluted with ether and
25 treated with 4N HCl in dioxane. A white solid formed which was collected by filtration. The solid was dried under vacuum (20 mm Hg) at room temperature for 18 h to give (0.70 g, 63%) of title compound (HCl salt) as a white solid.

30

mp 110-115°C.

MS (FAB, + ions) m/z 638(M + H).

Anal Calc'd for C₃₈H₃₀N₃O₄ + 1.0 H₂O + 1.0 HCl:

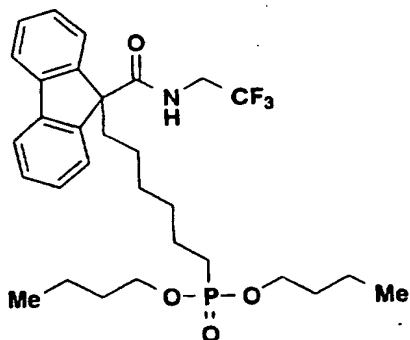
35

C, 64.21; H, 4.81; N, 6.07; F, 8.23

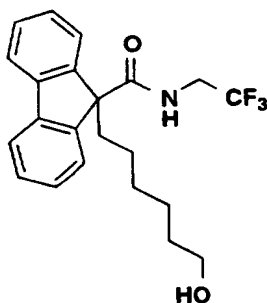
Found: C, 64.46; H, 4.88; N, 5.86; F, 8.13.

Example 292

[6-[9-[[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]hexyl]phosphonic acid, dibutyl ester



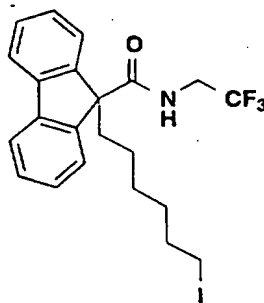
A.



To 400 mg (1.07 mmol) of Example 290 Part B compound was added 3.7 mL (1.87 mmol) of 9-BBN (9-borabicyclo[3.3.1]nonane, 0.5 M in THF). The reaction was stirred for 18 h, at which time it was cooled to 0°C and treated dropwise with 1.25 mL (3.74 mmol) of 3N NaOH and 432 µL (3.74 mmol) of 30% H₂O₂ simultaneously. The biphasic mixture was stirred vigorously for 18 h, at which time it was extracted with ethyl acetate and the organic layer was washed with H₂O, brine, dried (Na₂SO₄) and evaporated. Flash chromatography was performed on 100 g of silica gel eluting with 1:1 hexanes/ethyl acetate to provide 320 mg (77%) of title compound as a white solid.

25 MS (ES NH₃, + ions) m/z 409 (M + NH₄).

B.



5 To a solution of 310 mg (0.793 mmol) of Part A compound in 5 mL of THF, under argon at 0°C, was added 118 mg (1.74 mmol) of imidazole followed by 270 mg (1.03 mmol) of triphenylphosphine. The mixture was stirred for 0.5 h at which time 262 mg
10 (1.03 mmol) of iodine in 3 mL of THF was added dropwise. The reaction was stirred at 0°C for 1 h, room temperature for 1 h then diluted with hexanes. The organics were washed with fresh sodium bisulfite solution, NaHCO₃, water, brine, dried
15 (Na₂SO₄) and evaporated. Flash chromatography was performed on 25 g of silica gel eluting with 9:1 hexanes/ethyl acetate to provide 310 mg (78%) of title compound as a white solid.

20 C. [6-[9-[[[(2,2,2-Trifluoroethyl)amino]-carbonyl]-9H-fluoren-9-yl]hexyl]phosphonic acid, dibutyl ester

To 150 mg (0.30 mmol) of Part B compound was added 405 µL (1.50 mmol) of tributylphosphite
25 (neat). The mixture was heated to 120°C for 18 h and bulb to bulb distilled (5 mm, 100°C) to remove lower boiling impurities and provide 165 mg (98%) of title compound as a pale yellow oil.

30 MS (ES NH₃, + ions) m/z 568 (M + H).

Anal. Calcd. for $C_{30}H_{41}NO_4PF_3 + 0.24 CH_2Cl_2$:

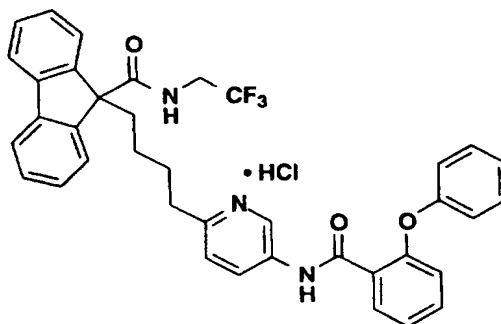
C, 61.77; H, 7.11; N, 2.38; P, 5.27; F, 9.69
Found: C, 61.80; H, 7.20; N, 2.36; P, 5.15; F, 9.60.

5

Example 293

9-[4-[5-[(2-Phenoxybenzoyl)amino]-2-pyridinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

10



Following the procedure in Example 274 Part C, Example 274 Part B compound (1.02 g, 2.19 mmol) was reacted with Example 275 Part A compound (prepared from 563 mg (2.63 mmol) of 2-phenoxybenzoic acid) to provide 712 mg of product as the free amine.

A portion of the desired product (317 mg) was dissolved in MeOH (2 mL) and a solution of 1.1N HCl/Et₂O (0.9 mL, 1.0 mmol) was added. The solution was concentrated in vacuo and the residue was triturated with Et₂O to give a foamy solid, which was pumped under high vacuum overnight to afford title compound (302 mg, 47%) as a foamy beige solid.

MS (ES, + ions) m/z 636 (M+H)

Anal. Calcd for $C_{38}H_{33}Cl_3N_3O_3 + 0.5H_2O$:

C, 67.01; H, 5.03; N, 6.17; Cl, 5.20;

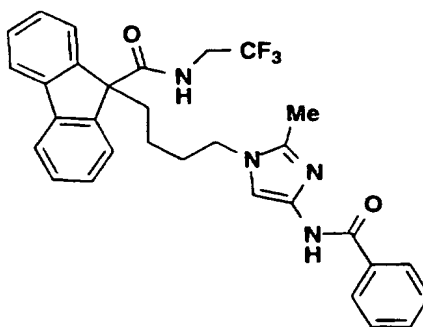
F, 8.37

Found: C, 67.04; H, 5.02; N, 6.03; Cl, 5.55;

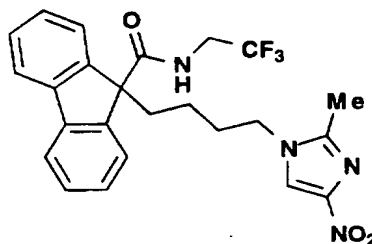
5 F, 8.20.

Example 294

9-[4-[4-(Benzoylamino)-2-methyl-1H-imidazol-1-yl]-
butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-
10 carboxamide



A.



15

To a solid mixture of Example 273 Part A(2) compound (1.00 g, 2.35 mmol), 2-methyl-5-nitroimidazole (400 mg, 3.15 mmol), and K_2CO_3 (2.82 mmol) was added DMF (5 mL) and the mixture was stirred at room temperature for 3 days. The reaction was partitioned between EtOAc and saturated $NaHCO_3$ and the organic layer was washed successively with H_2O and brine. The solution was dried (Na_2SO_4), filtered, and stripped. The residue was triturated with Et_2O /EtOAc/hexane to give title compound (973 mg, 88%) as a white solid. mp 145-147°C.

B. 9-[4-[4-(Benzoylamino)-2-methyl-1H-imidazol-1-yl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

5 A solution of compound Part A (171 mg, 0.36 mmol) in dry 1,4-dioxane (3.9 mL) was hydrogenated (balloon) over 10% Pd/C (35 mg) at room temperature for 5 hours. Additional 10% Pd/C (40 mg) was added and stirring over H₂ was continued for an
10 additional 16 hours. The reaction flask was evacuated and the atmosphere was replaced with air. To this slurry was added triethylamine (TEA) (200 µL, 145 mg, 1.4 mmol) followed by benzoyl chloride (100 µL). After one hour at room temperature, the
15 mixture was filtered through Celite, diluted with EtOAc and subsequently washed with saturated NaHCO₃, H₂O, and brine, then dried (Na₂SO₄), filtered, and stripped to give a brown oil. The residue was partially purified by flash
20 chromatography on silica gel (2/98-MeOH/CH₂Cl₂ as eluant). Further flash chromatographic separation (EtOAc as eluant) afforded title compound which was isolated as a light yellow solid foam by
trituration and stripping from EtOAc/hexanes (88
25 mg, 45%).

Anal. Calc'd for C₃₁H₂₉F₃N₄O₂•0.2H₂O+0.2C₆H₁₄:

C, 68.16; H, 5.72; N, 9.87; F, 10.04

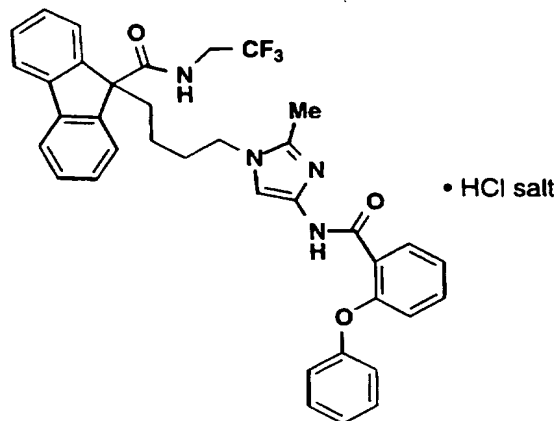
Found: C, 68.02; H, 5.76; N, 9.61; F, 9.65.

30

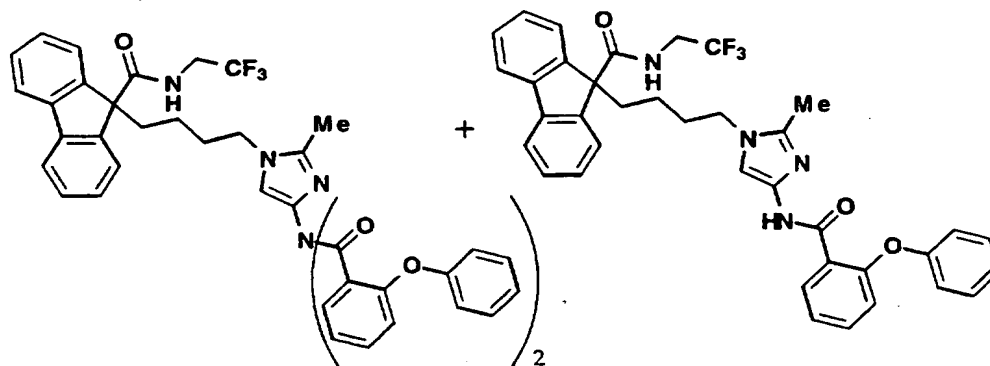
Example 295

9-[4-[4-[(2-Phenoxybenzoyl)amino]-2-methyl-1H-imidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

5



A. and B.



10

A solution of Example 294 Part A compound (350 mg, 0.65 mmol) in dry 1,4-dioxane (7 mL) was hydrogenated (balloon) over 10% Pd/C (126 mg) at room temperature for 28 hours. The reaction flask was evacuated and the atmosphere was replaced with air. To this slurry was added triethylamine (TEA) (300 μ L, 218 mg, 2.15 mmol) followed by 2-phenoxybenzoic acid chloride (320 mg, 1.37 mmol) in dry THF (2 mL). After 1.5 hours at room temperature, the mixture was filtered through Celite, diluted with EtOAc and subsequently washed with saturated NaHCO₃, H₂O, and brine, then dried (Na₂SO₄),

filtered, and stripped to give a brown oil. The residue was purified by flash chromatography on Merck SiO₂ (1:1-acetone:hexanes as eluant) to give a R_f 0.36 (1:1-acetone:hexanes) as a light brown foam (≈400 mg).

The mixture was separated by preparative HPLC (YMC-Pack ODS-A, 250 x 30 mm column, eluted with B:A solvent mixture, 50 to 100% B over a 20 minute linear gradient followed by 100% B (solvent A: 90% H₂O-10% MeOH-0.1% trifluoroacetic acid (TFA); solvent B: 10% H₂O-90% MeOH-0.1% TFA); flow rate 25 mL/min detecting at 254 nm). The desired fractions were stripped and the residues were partitioned between EtOAc and saturated NaHCO₃. The organic extracts were washed with brine, dried (Na₂SO₄), filtered and stripped to afford Part A compound (182 mg) and Part B compound (87 mg) as foams.

C. 9-[4-[4-[(2-Phenoxybenzoyl)amino]-2-methyl-1H-imidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

Part A compound (≈180 mg) was dissolved in MeOH (6 mL) and treated with K₂CO₃ (62 mg). HPLC analysis after 5 hours indicated that all of Part A compound was converted to Part B compound and 2-phenoxybenzoic acid methyl ester. The mixture was partitioned between EtOAc and H₂O. The organic layer was washed with H₂O and brine, then dried (Na₂SO₄), filtered and stripped. The residue was combined with Part B compound from above and flash chromatographed (SiO₂, 7/3-EtOAc/hexanes as eluant) to afford pure Part B compound as a pale yellow foam (210 mg, 51% from Example 294 Part A compound).

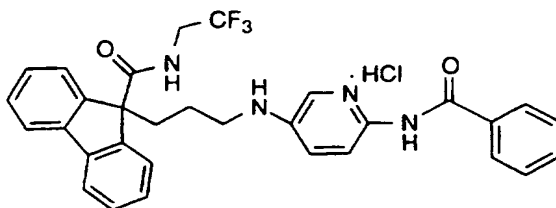
The foam was dissolved in THF (400 μ L), diluted with Et₂O (5 mL) and treated with 140 μ L of 4 N HCl in 1,4-dioxane. The resulting precipitate was collected by filtration and dried in vacuo to afford title compound as a white solid (212 mg, 48% from Example 294 Part A compound).

mp 200-202°C.

MS (ESI, + ions) m/z 639 (M+H)⁺; (ESI, - ions) m/z 637 (M-H)⁻.

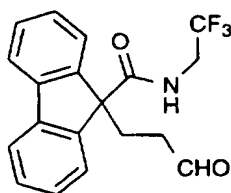
Example 296

9-[3-[[2-(Benzoylamino)-5-pyridinyl]amino]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride



contains 0.3 mole water, 0.1 mole ethyl acetate, and 0.3 mole ethyl ether

A.

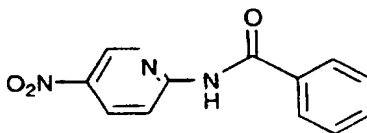


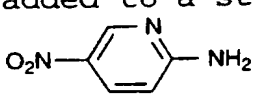
20

Ozone (Welsbach generator) was bubbled through a stirred solution of 2.07 g (6 mmol) of Example 291 Part B compound in 25 mL of dry MeOH at -65°C for 45 min. Nitrogen was bubbled through the solution for 10 min, 5 mL of dimethyl sulfide was added, and the reaction was warmed to room temperature. The solvent was removed and the residue was taken up in EtOAc. The EtOAc was washed with water (3x), dried (Na₂SO₄) and

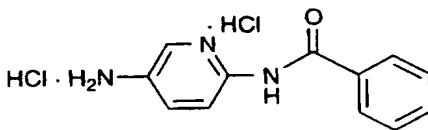
concentrated to an oil (2.21 g). Chromatography of the oil over 150 g of silica gel packed in 1% EtOAc in CH₂Cl₂, by elution with 2% EtOAc in CH₂Cl₂, afforded 1.11 g (53%) of title compound as an oily residue.

B.



10 Benzoyl chloride (8.2 mL, 70 mmol) was added to a stirred suspension of 7.5 g (54 mmol) of  and 13 mL (160 mmol) of dry pyridine in 50 mL of dry THF and the mixture was stirred for 20 h at room temperature. The reaction was
15 filtered and the filtrate was concentrated to a gummy residue, which was slurried with CH₂Cl₂, water, and 10% aq. NaHCO₃ to give crystals. The crystals were collected by filtration, washed with CH₂Cl₂, and dried to give 7.44 g pale yellow
20 crystals, which were recrystal-lized from hot 95% EtOH to give 7.18 g of pale yellow crystalline title compound (55%) having mp 169-170°C.

C.

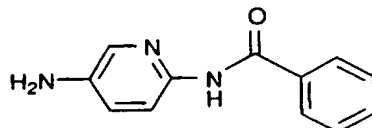


25

Part B compound (2.92 g, 12 mmol) was hydrogenated with 360 mg of 10% Pd/C in 50 mL of AcOH at 1 atmosphere for 1.5 h. Concentrated HCl
30 (2.1 mL, 24.5 mmol) was added and the solids were collected by filtration. Trituration of the wet moist solid with EtOH and then filtration through a

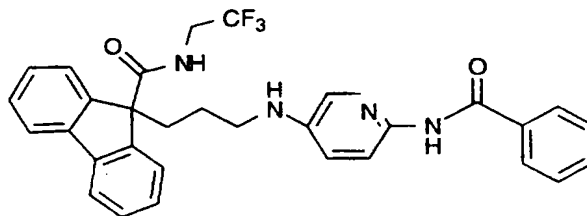
45 μ nylon filter gave a filtrate, which was concentrated to a 25 mL yellow slurry. Et₂O (150 mL) was added and the solids were collected, washed with Et₂O, and dried for 2 h to give 2.77 g (81%) of title compound as a solid.

D.



Part C compound (286 mg, 1 mmol) was dissolved in water and layered with CH₂Cl₂. Aqueous 5% NaHCO₃ was added and after extracting, the CH₂Cl₂ layer was washed with 5% NaHCO₃ and then water (2x), dried (Na₂SO₄), and concentrated to give 189 mg (89%) of title compound as an amorphous pale yellow solid.

E.



Acetic acid (0.29 mL, 5.1 mmol) was added to a stirred suspension of 180 mg (0.85 mmol) of Part D compound and 297 mg (0.85 mmol) of Part A compound in 5 mL of 1,2-dichloroethane. After 5 min, NaBH(OAc)₃ (540 mg, 2.55 mmol) was added to the clear solution and the reaction was stirred for 16 h at room temperature. The reaction was diluted with CH₂Cl₂ and 5% NaHCO₃ and the layers were separated. The CH₂Cl₂ was washed with 5% NaHCO₃ and water (2x), dried (Na₂SO₄), and concentrated to a foam (479 mg). Chromatography of this foam over a column of silica gel (40 g) packed in CH₂Cl₂, by

eluting with CH₂Cl₂-MeOH (97:3), gave 429 mg of
impure title compound. Chromatography of the 429
mg sample over 40 g of silica gel using CH₂Cl₂-
EtOAc (8:2) gave 246 mg (53%) of title compound as
5 a gummy residue.

F. 9-[3-[[2-(Benzoylamino)-5-pyridinyl]-
amino]propyl]-N-(2,2,2-trifluoroethyl)-9H-
fluorene-9-carboxamide, monohydrochloride

10 To a solution of Part E compound (243 mg,
0.446 mmol) in 3 mL of dry THF was added 0.4 mL of
4 N HCl in dioxane (1.6 mmol). Ether was added to
the clear solution and the precipitate was
collected, washed with Et₂O, and dried at 40°C/0.5
15 mm for 4 h to give 225 mg (82%) title compound as a
pale yellow solid having mp 120-126°C.

MS (ESI-NH₃, + ions) 545 (M+H); (- ions) 543 (M-H).

20 Anal. Calcd for C₃₁H₂₇F₃N₄O₂ + HCl + 0.3 H₂O + 0.1
EtOAc + 0.3 Et₂O:

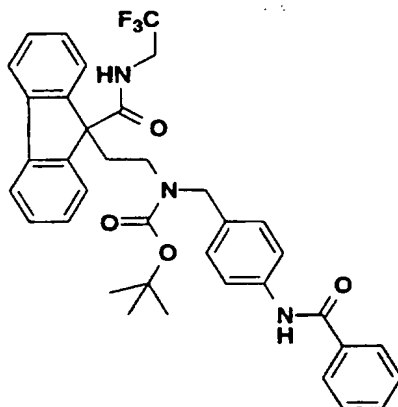
C, 63.41; H, 5.29; N, 9.07; Cl, 5.74; F,
9.23 Found: C, 63.40; H, 5.25; N, 8.88; Cl,
5.60; F, 9.10.

25

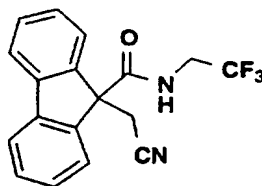
Example 297

[[4-(Benzoylamino)phenyl]methyl][2-[9-[(2,2,2-tri-
fluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]ethyl]-
carbamic acid, 1,1-dimethylethyl ester

5



A.

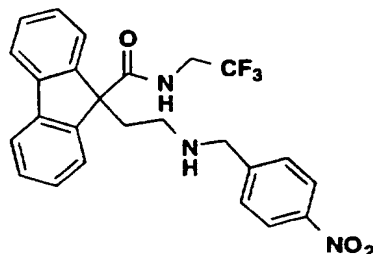


10

Butyllithium (18 mL, 2.5M in hexanes, 44 mmol) was added dropwise over 10 min to a solution of 9-fluorenicarboxylic acid (4.2 g, 20 mmol) in THF (200 mL) at 0°C under argon. The slightly
15 heterogeneous dark yellow reaction was stirred at 0°C for 30 min, then chloroacetonitrile (1.5 mL, 24 mmol) was added dropwise over 3 min. The orange reaction was stirred at 0°C for 30 min, warmed to room temperature and stirred for 3 h. The reaction
20 was extracted with water (2 x 100 mL) and the combined aqueous extracts were washed with Et₂O (100 mL). The aqueous layer was acidified to pH<2 with 1N HCl and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were dried over
25 MgSO₄, filtered, and concentrated in vacuo to give 4.7 g of a light yellow solid (mp 138-145°C).

A portion (2.63 g) of the crude carboxylic acid was dissolved in CH_2Cl_2 (30 mL) under argon. N,N-Dimethylformamide (40 μL , 0.53 mmol) was added followed by oxalyl chloride (8.0 mL, 2.0M in CH_2Cl_2 , 15.9 mmol). The reaction bubbled for a few minutes and was allowed to stir at room temperature for 1.5 h. The reaction was concentrated in vacuo then pumped under high vacuum to give the crude acid chloride. Triethylamine (4.4 mL, 31.8 mmol) was added to a suspension of 2,2,2-trifluoroethylamine hydrochloride (1.71 g, 12.7 mmol) in CH_2Cl_2 (20 mL) at 0°C under argon. The resulting thick slurry was stirred at 0°C for 5 min, then a solution of the crude acid chloride in CH_2Cl_2 (10 mL) was added dropwise over 5 min. The reaction was stirred at 0°C for 10 min, diluted with CH_2Cl_2 (50 mL), washed with 1N HCl (2 x 20 mL) and saturated NaHCO_3 (30 mL), then dried over Na_2SO_4 . Evaporation gave 3.5 g of a yellow foam which was purified by flash chromatography on silica (150 g) eluting with CH_2Cl_2 to give title compound (2.74 g, 76%) as a white solid (mp 159-159.5).

B.



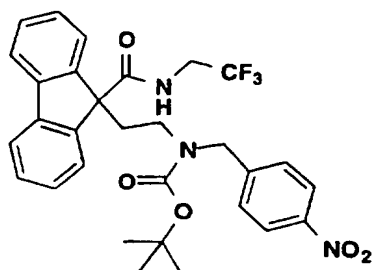
25

To a solution of Part A compound (2.7 g, 8.2 mmol) in methanol (30 mL) and chloroform (1.3 mL, 16 mmol) was added platinum oxide (186 mg, 0.82 mmol). The reaction mixture was hydrogenated (balloon) for 3.5 days, filtered through Celite and concentrated in vacuo to give 3.13 g of the crude amine hydrochloride.

4-Nitrobenzyl bromide (1.57 g, 7.3 mmol) was added to a stirred solution of the crude amine hydrochloride (2.7 g, 7.3 mmol) and triethylamine (1.0 ml, 7.3 mmol) in THF (15 ml) at 0°C. The reaction stirred under argon in a melting ice bath overnight. Reaction mixture partitioned between ethyl acetate and saturated sodium bicarbonate solution. Aqueous layer extracted one time with ethyl acetate. The combined organic layers were dried (Na₂SO₄), and the solvent removed *in vacuo* to give a yellow oil which was purified by flash chromatography (SiO₂, 400g) packed and run with 30% EtOAc in methylene chloride to give title compound as a clear oil (940 mg, 27.5% yield).

15

C.



To the yellow solution of Part B compound (900 mg, 1.9 mmol) and 4-dimethylaminopyridine (280 mg, 2.3 mmol) in methylene chloride (10 ml) was added di-tert-butylidicarbonate (500 mg, 2.3 mmol) and the reaction stirred under argon at room temperature 1.5 h. More di-tert-butylidicarbonate (85 mg, 0.46 mmol) was added and the reaction stirred 1 h. The reaction was partitioned between methylene chloride and brine. The organic layer was dried (Na₂SO₄) and the solvent removed *in vacuo* to give a yellow oil which was purified by flash chromatography (SiO₂, 100g) packed and run with 5% EtOAc in methylene chloride to give title compound as a solid white foam (944 mg, 86.6% yield).

D. [[4-(Benzoylamino)phenyl]methyl][2-[9-
[[[(2,2,2-trifluoroethyl)amino]carbonyl]-9H-
fluoren-9-yl]ethyl]carbamic acid, 1,1-
5 dimethylethyl ester

10 10% Palladium on carbon (200 mg, catalyst)
was added to a solution of Part C compound (860 mg,
1.5 mmol) in EtOAc (10ml) and the mixture
hydrogenated (balloon) for 2h. The reaction was
10 filtered through Celite and the Celite rinsed with
EtOAc. A portion of the resulting amine solution
(32 ml) was used in the next reaction.

To the amine solution (15 ml, ~0.71 mmol)
cooled to -5°C was added triethylamine (99 µl, 0.71
15 mmol) followed by benzoyl chloride (82 µl, 0.71
mmol). The reaction was stirred at -5°C under
argon for 2 h. The reaction mixture was
partitioned between ethyl acetate and water. The
organic layer was dried (Na₂SO₄) and the solvent
20 removed in vacuo to give a clear oil which was
purified by flash chromatography (SiO₂, 50 g)
packed and run with 30% EtOAc in hexanes to give
title compound as a solid white foam (369 mg, 80.9%
yield).

25

mp 96-98°C.

MS (ESI, + ions) m/z 644 (M + H).

Anal. calc'd for C₃₇H₃₆F₃N₃O₄:

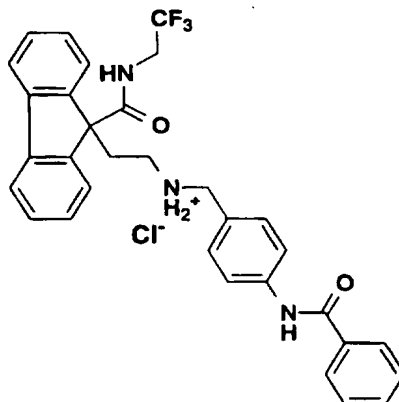
30 C, 69.04; H, 5.64; N, 6.53

Found: C, 68.94; H, 5.65; N, 6.27.

Example 298

9-[2-[[[4-(Benzoylamino)phenyl]methyl]amino]ethyl]-
N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,
monohydrochloride

5



A solution of Example 297 compound (264 mg, 0.41 mmol) in 1.1 ml 4.0M HCl in dioxane was
10 stirred under argon at room temperature for 2h. The solvent was removed *in vacuo* at 30°C. The residue was mixed with toluene, and the toluene removed *in vacuo* to give title compound as a white solid (193 mg, 81.1% yield).

15

mp 135-38°C.

MS (ESI, + ions) m/z 544 (M + H); 1087 (2M + H).

Anal. calc'd for C₃₂H₂₈F₃N₃O₂ + 1HCl + 0.1 dioxane +
20 0.1 toluene:

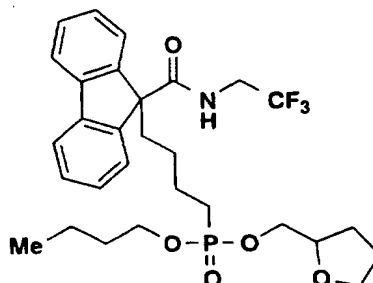
C, 65.49; H, 5.25; N, 6.92

Found: C, 65.54; H, 5.50; N, 6.66.

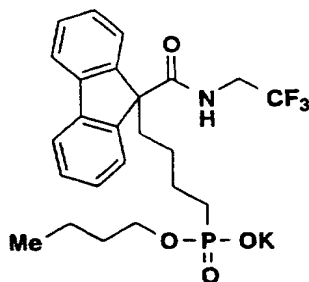
Example 299

9-[4-[Butoxy(tetrahydrofuran-2-ylmethoxy)-
phosphinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-
fluorene-9-carboxamide

5



A.



10

To a solution of 1 g (1.85 mmol) of Example 186 compound in 10 mL of a 3:7 water/n-butanol solution was added 1 g (18.50 mmol) of KOH pellets. The mixture was heated to 100°C for 5 days, at which time it was evaporated to remove n-butanol and freeze dried. The residue was purified by MPLC on a column of CHP20P gel (2.5 cm diam. X 20 cm height) eluting with water (1 L) followed by a gradient created by the gradual addition of 500 mL of acetonitrile to a reservoir of 700 mL of water. Fractions #34 to 40 were pooled. The acetonitrile was removed under reduced pressure and the aqueous solution was freeze dried to provide 695 mg (72%) of title compound as a white lyophilate.

TLC: silica gel (8:1:1 n-propanol/water/aqueous NH₃) R_f=0.63.

MS ((ES-NH₄OH, + ions) m/z 525 (M+H+CH₃CN), 501
(M+NH₄), 484 (M+H).

Anal. Calcd for C₂₄H₂₈NO₄PF₃K + 0.93 H₂O.

C, 53.56; H, 5.59; N, 2.60; P, 5.75

5 Found: C, 53.60; H, 5.56; N, 2.56; P, 5.78.

B. 9-[4-[Butoxy(tetrahydrofuran-2-ylmethoxy)phosphinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-
10 carboxamide

To a solution of 200 mg (0.38 mmol) of Part A compound in 3 mL of toluene, under argon at room temperature, was added dropwise 53 μ L (0.73 mmol) of triethylamine followed by 146 μ L (1.15 mmol) of
15 chlorotrimethylsilane. The reaction was stirred for 1 h at which time it was evaporated to dryness to provide a pale yellow solid. The solid was dissolved in 3 mL of dichloromethane, under argon at room temperature, and treated with two drops of
20 DMF followed by the dropwise addition of 283 μ L (0.57 mmol) of oxalyl chloride (2.0 M in dichloromethane). The reaction was stirred for 0.5 h at which time it was evaporated to dryness to provide a yellow solid. The solid was dissolved in
25 3 mL of THF, under argon at room temperature, and treated dropwise with 58 μ L (0.57 mmol) of tetrahydrofurfuryl alcohol and 31 μ L (0.38 mmol) of pyridine. The reaction was stirred for 18 h at which time it was diluted with ether and washed
30 with NaHCO₃, brine, dried (Na₂SO₄) and evaporated. Flash chromatography was performed on 75 g of silica gel eluting with 97:3 dichloromethane/isopropanol to provide 75 mg (35%) of title compound as a pale yellow oil.

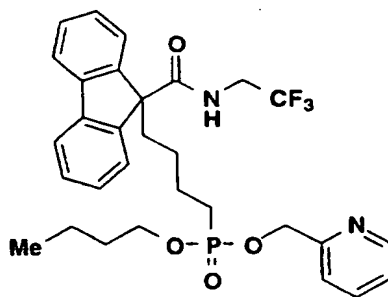
35

MS (FAB, \pm ions) m/z 568 (M + H), (FAB, - ion) 566 (M - H).

HRMS molecular ion calcd for $C_{29}H_{38}NO_5PF_3$ (M + H)
568.24398, found 568.2440.

Example 300

- 5 9-[4-[Butoxy(2-pyridinylmethoxy)phosphinyl]butyl]-
N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



10

- To a solution of 200 mg (0.38 mmol) of
Example 299 Part A compound in 3 mL of toluene,
under argon at room temperature, was added dropwise
53 μ L (0.73 mmol) of triethylamine followed by 146
15 μ L (1.15 mmol) of chlorotrimethylsilane. The
reaction was stirred for 1 h at which time it was
evaporated to dryness to provide a pale yellow
solid. The solid was dissolved in 3 mL of
dichloromethane, under argon at room temperature,
20 and treated with two drops of DMF followed by the
dropwise addition of 290 μ L (0.58 mmol) of oxalyl
chloride (2.0 M in dichloromethane). The reaction
was stirred for 0.5 h at which time it was
evaporated to dryness to provide a yellow solid.
25 The solid was dissolved in 3 mL of THF, under argon
at RT, and treated dropwise with 73 μ L (0.77 mmol)
of 2-pyridylcarbinol. The reaction was stirred for
18 h at which time it was diluted with ether and
washed with $NaHCO_3$, brine, dried (Na_2SO_4) and
30 evaporated. Flash chromatography was performed on
65 g of silica gel eluting with 97:3

dichloromethane/isopropanol to provide 160 mg (73%) of title compound as a pale yellow oil.

MS (ES-NH₄OH, \pm ions) m/z 575 (M + H).

5

Anal. Calcd. for C₃₀H₃₄N₂O₄PF₃ + 0.65H₂O:

C, 61.46; H, 6.07; N, 4.78; F, 9.72; P,

5.28.

Found: C, 61.07; H, 5.88; N, 5.00; F, 9.55; P,

10 5.26.

The following additional compounds of the invention were prepared following the procedures set out herein.

15

Example 301

9-[4-(Dipropoxyphosphinyl)butyl]-N-(2,2,2-trifluoro-ethyl)-9H-fluorene-9-carboxamide

20 MS (ES-NH₄OH, + ions) m/z 529 (M+NH₄), 512 (M+H).

Anal. Calc'd for C₂₆H₃₃N₄PF₃ + 0.23 CH₂Cl₂:

C, 59.32; H, 6.35; N, 2.64; P, 5.83

Found: C, 59.31; H, 6.46; N, 2.88; P, 5.68.

25

Example 302

9-[4-[4-[[4-Nitrophenyl)sulfonyl]amino]phenyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

30 mp 136-138°C.

MS (ES, - ions) m/z 622 (M-H).

Anal. Calc'd for C₃₂H₂₈N₃SO₅F₃ + 2.00 CH₂Cl₂:

C, 51.60; H, 4.06; N, 5.30; S, 4.04

Found: C, 51.70; H, 4.00; N, 5.20; S, 4.17.

35

Example 303

9-[4-[4-[[(2-Nitrophenyl)sulfonyl]amino]phenyl]-
butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-
carboxamide

5

mp 60-64°C.

MS (ES, - ions) m/z 622 (M-H).

Anal. Calc'd for $C_{32}H_{28}N_3SO_5F_3 + 0.5 CH_2Cl_2$:

C, 58.60; H, 4.39; N, 6.31; S, 4.81

10 Found: C, 58.61; H, 4.41; N, 6.14; S, 4.88.

Example 304

9-[4-(Dibutoxyphosphinyl)butyl]-3,6-difluoro-N-
(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

15

MS (ESI, M+H)⁺ = 576 m/z⁺.

Anal. Calc'd for $C_{28}H_{35}F_5NO_4P \cdot 0.25 H_2O$:

C, 57.98; H, 6.17; N, 2.41

Found: C, 57.95; H, 6.22; N, 2.23.

20

Example 305

9-[3-[[5-[(2-Phenoxybenzoyl)amino]-2-pyridinyl]-
oxylpropyl]-N-propyl-9H-fluorene-9-carboxamide

25 mp 104-108°C.

MS (FAB, + ions) m/z 598 (M+H).

Anal. Calc'd for $C_{38}H_{35}N_3O_4$:

C, 76.36; H, 5.90; N, 7.03

Found: C, 75.86; H, 5.80; N, 6.96.

30

Example 306

9-[6-[(6-Ethoxy-2-benzothiazolyl)thio]hexyl]-N-
(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

35 MS (FAB, + ions) m/z 585 (M+H).

Anal. Calc'd for $C_{31}H_{31}N_2O_2S_2F_3$:

C, 63.68; H, 5.34; N, 4.79; F, 9.75

Found: C, 63.43; H, 5.37; N, 4.61; F, 9.78.

5

Example 307

[4-[9-[[2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]-butylphosphonic acid, di(1-methylethyl) ester

10 mp 91-94°C.

MS (ES-NH₄OH, + ions) m/z 512 (M+H).

Anal. Calc'd for $C_{26}H_{33}NO_4PF_3 + 0.13 CH_2Cl_2$:

C, 60.06; H, 6.42; N, 2.68; P, 5.93;

F, 10.91

15 Found: C, 60.21; H, 6.70; N, 2.68; P, 6.00;

F, 10.64.

Example 308

20 [[4-[(2-Phenoxybenzoyl)amino]phenyl]methyl][2-[9-[[2,2,2-trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]ethyl carbamic acid, 1,1-dimethylethyl ester

mp 83-85°C.

MS (ESI, + ions) m/z 753 (M+NH₄).

25 Anal. Calc'd for $C_{43}H_{40}F_3N_3O_5 + 1.4 H_2O$:

C, 67.87; H, 5.67; N, 5.52

Found: C, 67.85; H, 5.34; N, 5.42.

Example 309

30 9-[2-[[[4-[(2-Phenoxybenzoyl)amino]phenyl]methyl]-amino]ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

mp 260-62°C.

35 MS (ESI, + ions) m/z 636 (M+H).

Anal. Calc'd for $C_{38}H_{32}F_3N_3O_3 \cdot HCl$:

C, 67.90; H, 4.95; N, 6.25

Found: C, 56.06; H, 4.07; N, 4.93.

5

Example 310

[1-[4-[9-[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]butyl]-1H-imidazol-4-yl]carbamic acid, 1,1-dimethylethyl ester

10 MS (ESI, + ions) m/z 543 (M+H)⁺; (ESI, - ions) m/z 541 (M-H)⁻.

Anal. Calc'd for $C_{29}H_{33}F_3N_4O_3 + 0.1 C_6H_{14}$:

C, 64.50; H, 6.29; N, 10.16; F, 10.34

Found: C, 64.18; H, 6.39; N, 9.86; F, 9.54.

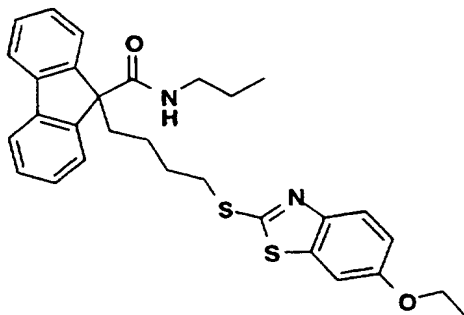
15

The following Examples 311 to 313 describe preparation of compounds of the invention employing solid phase synthesis techniques as described hereinafter.

20

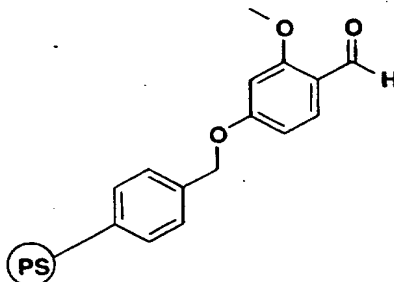
Example 311

9-[4-[(6-Ethoxy-2-benzothiazolyl)thio]butyl]-N-propyl-9H-fluorene-9-carboxamide



25

A.



(PS) = 1% Divinylbenzene cross-linked polystyrene resin, 100-200 mesh

- 5 To a magnetically stirred suspension of 4.8 g (120 mmol, 10 eq) of sodium hydride (60% mineral oil dispersion) in 30 mL of dimethylformamide (DMF) at 0 °C was added a solution of 18.2 g (120 mmol, 10 eq) of 4-hydroxy-2-methoxybenzaldehyde in 50 mL
- 10 of DMF dropwise over 75 min. The reaction was allowed to warm to room temperature (RT) and stirred for an additional 75 min. The stirbar was removed and 10 g (12 mmol, 1 eq) of Merrifield resin (loading of 1.2 mmol/g, Advanced Chemtech)
- 15 was added. The flask was placed in a heating mantel mounted on a vortex mixer and heated at 70°C (internal temperature) while vortexing for 26 h. The contents of the reaction vessel were transferred to a large filter funnel with a
- 20 scintered-glass frit (porosity C) and rinsed sequentially with DMF (3 x 100 mL), 1:1 DMF:water (3 x 100 mL), water (2 x 100 mL) and MeOH (5 x 100 mL). The resin was dried under high vacuum (0.1 mm Hg) for 72 h to afford 11.16 g (98% of expected
- 25 weight) of title product as a tacky non-freeflowing tan resin. The resin was characterized by gel-phase ¹³C-NMR and elemental analysis (chlorine and oxygen).

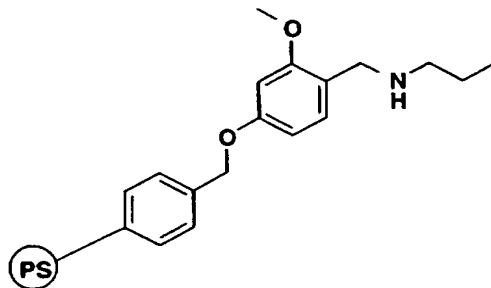
Elemental Analysis:

Chlorine: Expected 0% Cl for 100% loading; found 0.21%. Starting Cl content of resin was 4.26%.

Residual Cl consistent with 95% resin loading.

5 Oxygen: Expected 5.76% for 100% loading; found 6.21%.

B.



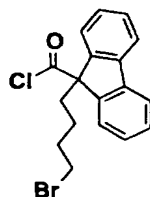
10

To a 25 mL Varian polypropylene tube fitted with a polyethylene frit and a luer stopcock was added 500 mg of Part A resin. The tube was sealed with a 19 mm Aldrich Suba septa and the resin was swollen in 5 mL of dry DMF, mixed by vortexing for 1 min and the DMF was removed using vacuum and N₂ pressure in order to maintain the vessel under inert atmosphere. Trimethyl orthoformate (1 mL) was added followed by 3.2 mL of DMF and 0.8 mL (10.0 mmol, 18 eq) of n-propylamine. The reaction mixture was vortexed for 18 h at room temperature. After removal of the reaction solution by nitrogen pressure and vacuum, 5 mL of a 200 mg/mL solution of sodium triacetoxyborohydride in DMF (1 g, 4.7 mmol, 8 eq) and 100 μ L of acetic acid were added. The reaction mixture was vortexed for 8 h at room temperature. The reaction solution was removed and the resin was rinsed with DMF (4 x 5 mL), 1:1 DMF:water (2 x 5 mL), water (1 x 5 mL), DMF (3 x 5 mL) and dichloromethane (CH₂Cl₂) (4 x 5 mL). The last CH₂Cl₂ rinse was done with dry CH₂Cl₂ in the tube with the septa in place using nitrogen gas and

vacuum to filter away the solvent and keep the reaction vessel under inert atmosphere. The title resin was used in the next step without characterization.

5

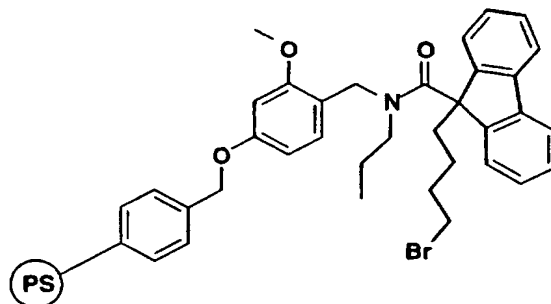
C.



To 3.45 g (10 mmol, 1 eq) of Example 273 Part A(1) compound in 15 mL of CH_2Cl_2 was added 100 μL of DMF. The resulting solution was cooled to 0°C and 7.5 mL (15 mmol, 1.5 eq) of a 2.0 M oxalyl chloride solution in CH_2Cl_2 was added. The bubbling reaction mixture was stirred at 0°C for 15 min and then allowed to warm to room temperature. After 2 h, the reaction mixture was concentrated to afford the crude acid title chloride as a yellowish orange solid/oil mixture which was dissolved in CH_2Cl_2 and used without purification.

20

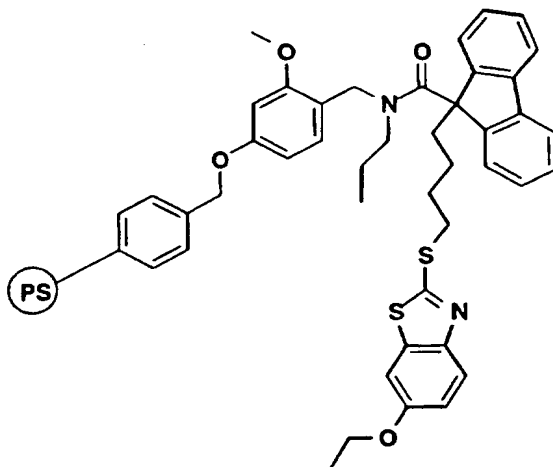
D.



To the Part B resin in the polypropylene tube were added 1 mL of diisopropylethyl amine (5.7 mmol, 10 eq) and 1 mL of CH_2Cl_2 and the resulting mixture was mixed for 2 min. The tube was cooled to 0°C in an ice bath and 4 mL (2.2 mmol, 4 eq) of

a solution of Part C acid chloride in CH_2Cl_2 was added. The resulting orange reaction mixture was mixed by vortexing at room temperature for 19 h. and then rinsed with CH_2Cl_2 (4 x 5 mL) to afford
5 title resin which was used in the next step without characterization.

E.



10

The Part D resin in the sealed polypropylene tube was swollen in 5 mL of dry DMF and vortexed for 2 min. The solvent was removed with N_2 and vacuum and a solution of 1.16 g (5.5
15 mmol, 10 eq) of 6-ethoxy-2-mercaptobenzothiazole in 4 mL of DMF was added to the resin followed by 5 mL (5 mmol, 9 eq) of a 1.0 M solution of sodium bistrimethylsilylamide in THF. Vortexing was initiated and the reaction mixture was mixed for 17
20 h at room temperature. The reaction solution was filtered away and the title resin was rinsed with DMF (4 x 5 mL), 1:1 DMF:water (2 x 5 mL), water (1 x 5 mL), DMF (3 x 5 mL) and dichloromethane (CH_2Cl_2) (4 x 5 mL).

25

F. 9-[4-[(6-Ethoxy-2-benzothiazolyl)thio]-
butyl]-N-propyl-9H-fluorene-9-carboxamide

The Part E resin was treated with 5 mL of 100% trifluoroacetic acid and vortexed for 90 min.
5 The reaction solution was collected, the resin was rinsed with CH₂Cl₂ (3 x 1 mL) and the combined reaction solution and rinses were concentrated. The products from 3 parallel reactions were each redissolved in 15 mL of CH₂Cl₂, pooled and
10 reconcentrated to afford 393 mg (46% crude) of an off-white solid. Recrystallization from MeOH afforded 339 mg (40%) of title compound as a white solid.

15 mp 112-113.5°C.

MS (electrospray, pos. ions): m/z 517 (M+H).

Anal. Calcd for C₃₀H₃₂N₂O₂S₂:

C, 69.73; H, 6.24; N, 5.42; S, 12.41

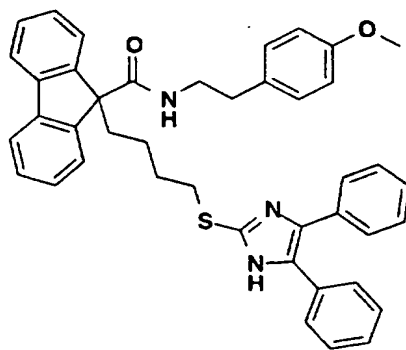
Found: C, 69.48; H, 6.22; N, 5.39; S, 12.25.

20

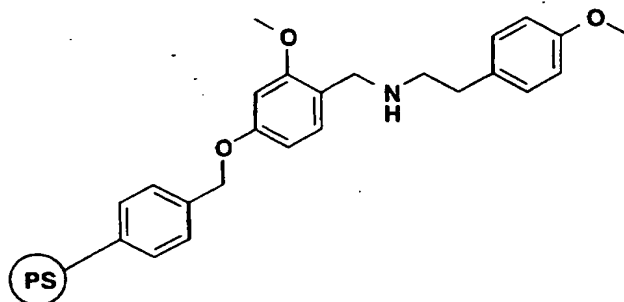
Example 312

9-[4-[(4,5-Diphenyl-1H-imidazol-2-yl)thio]butyl]-N-
[2-(4-methoxyphenyl)ethyl]-9H-fluorene-9-
carboxamide

25



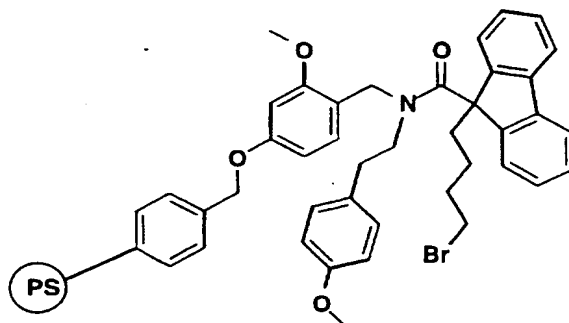
A.



To a 25 mL Varian polypropylene tube fitted
5 with a polyethylene frit and a luer stopcock was
added 500 mg of Example 311 Part A resin. The tube
was sealed with a 19 mm Aldrich Suba septa and the
resin was swollen in 5 mL of dry DMF, mixed by
vortexing for 1 min and the DMF was removed using
10 vacuum and N₂ pressure in order to maintain the
vessel under inert atmosphere. Trimethyl orthoformate
(1 mL) was added followed by 2.6 mL of DMF and
1.46 mL (1.51 g, 10.0 mmol, 18 eq) of *p*-methoxy-
phenethylamine. The reaction mixture was vortexed
15 for 18 h at RT. After removal of the reaction
solution by nitrogen pressure and vacuum, 5 mL of a
200 mg/mL solution of sodium triacetoxyborohydride
in DMF (1 g, 4.7 mmol, 8 eq) and 100 µL of acetic
acid were added. The reaction mixture was vortexed
20 for 8 h at room temperature. The reaction solution
was removed and the resin was rinsed with DMF (4 x
5 mL), 1:1 DMF:water (2 x 5 mL), water (1 x 5 mL),
DMF (3 x 5 mL) and dichloromethane (CH₂Cl₂) (4 x 5
mL). The last CH₂Cl₂ rinse was done with dry CH₂Cl₂
25 in the tube with the septa in place using nitrogen
gas and vacuum to filter away the solvent and keep
the reaction vessel under inert atmosphere. The
title resin was used in the next step without
characterization.

30

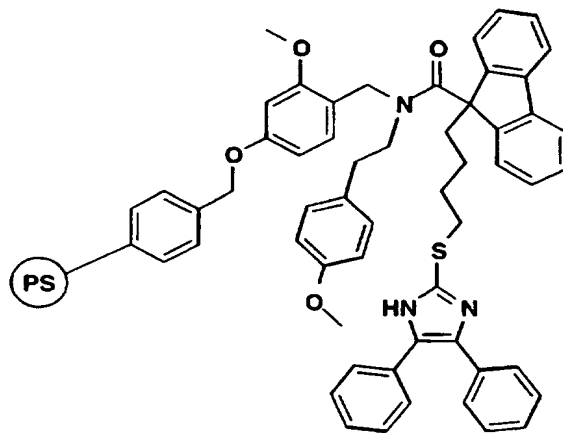
B.



To the Part A resin in the polypropylene
 5 tube were added 1 mL of diisopropylethyl amine (5.7
 mmol, 10 eq) and 1 mL of CH_2Cl_2 and the resulting
 mixture was mixed for 2 min. The tube was cooled
 to 0°C in an ice bath and 4 mL (2.2 mmol, 4 eq) of
 10 a solution of Example 311 Part C acid chloride in
 CH_2Cl_2 was added. The resulting orange reaction
 mixture was mixed by vortexing at room temperature
 for 19 h and then rinsed with CH_2Cl_2 (4 x 5 mL) to
 afford title resin which was used in the next step
 without characterization.

15

C.



The Part B resin in the sealed
 20 polypropylene tube was swollen in 5 mL of dry DMF
 and vortexed for 2 min. The solvent was removed
 with N_2 and vacuum. To a suspension of 1.4 g (5.5

mmol, 10 eq) of 4,5-diphenyl-2-imidazolethiol in 5 mL of DMF was added 5 mL (5 mmol, 9 eq) of a 1.0 M solution of sodium bistrimethylsilylamide in THF. The resulting solution of thiolate anion was added to the resin, vortexing was initiated and the reaction mixture was mixed for 17 h at RT. The reaction solution was filtered away and the title resin was rinsed with DMF (4 x 5 mL), 1:1 DMF:water (2 x 5 mL), water (1 x 5 mL), DMF (3 x 5 mL) and dichloromethane (CH₂Cl₂) (4 x 5 mL) and used in the next step without characterization.

D. 9-[4-[(4,5-Diphenyl-1H-imidazol-2-yl)-thio]butyl]-N-[2-(4-methoxyphenyl)ethyl]-9H-fluorene-9-carboxamide

The Part C resin was treated with 5 mL of 100% trifluoroacetic acid and vortexed for 90 min. The reaction solution was collected, the resin was rinsed with CH₂Cl₂ (3 x 1 mL) and the combined reaction solution and rinses were concentrated. The products from 3 parallel reactions were each redissolved in 15 mL of CH₂Cl₂, pooled and reconcentrated to afford 729 mg (68% crude) of a yellow oil. Flash chromatography on silica gel (50 g) eluted with 2% MeOH in CH₂Cl₂ (1 L), followed by 5% MeOH in CH₂Cl₂ (1 L) afforded 208 mg (19%) of title compound as a white foam.

MS(electrospray, pos. ions): m/z 650 (M + H).

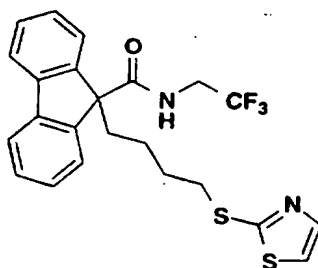
Anal. Calc'd for C₄₂H₃₉N₃O₂S + 0.63 CH₂Cl₂:

C, 71.72; H, 5.59; N, 5.97; S, 4.56

Found: C, 71.96; H, 5.64; N, 5.94; S, 4.76.

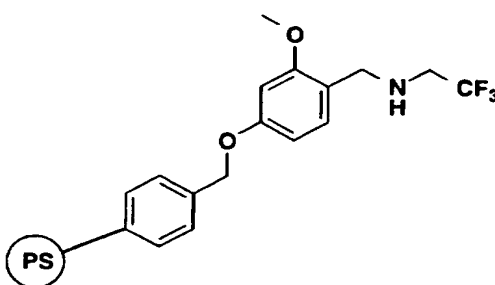
Example 313

9-[4-(2-Thiazolylthio)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



5

A.

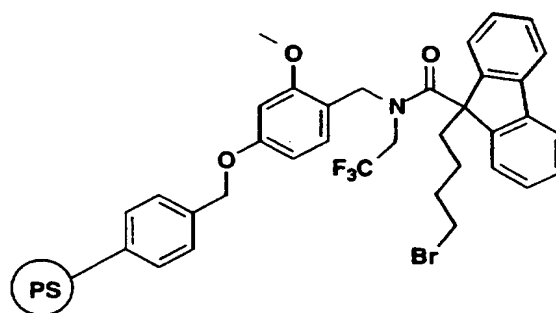


- 10 To a 25 mL Varian polypropylene tube fitted with a polyethylene frit and a luer stopcock was added 500 mg of Example 311 Part A resin. The tube was sealed with a 19 mm Aldrich Suba septa and the resin was swollen in 5 mL of dry DMF, mixed by
- 15 vortexing for 1 min and the DMF was removed using vacuum and N₂ pressure in order to maintain the vessel under inert atmosphere. Trimethyl orthoformate (1 mL) was added followed by 3.2 mL of DMF and 796 µL (991 mg, 10.0 mmol, 18 eq) of 2,2,2-trifluoroethylamine. The reaction mixture was
- 20 vortexed for 18 h at room temperature. After removal of the reaction solution by nitrogen pressure and vacuum, 5 mL of a 200 mg/mL solution of sodium triacetoxyboro-hydride in DMF (1 g, 4.7 mmol, 8 eq) and 100 µL of acetic acid were added.
- 25 The reaction mixture was vortexed for 8 h at room temperature. The reaction solution was removed and

the resin was rinsed with DMF (4 x 5 mL), 1:1 DMF:water (2 x 5 mL), water (1 x 5 mL), DMF (3 x 5 mL) and dichloromethane (CH₂Cl₂) (4 x 5 mL). The last CH₂Cl₂ rinse was done with dry CH₂Cl₂ in the tube with the septa in place using nitrogen gas and vacuum to filter away the solvent and keep the reaction vessel under inert atmosphere. The title resin was used in the next step without characterization.

10

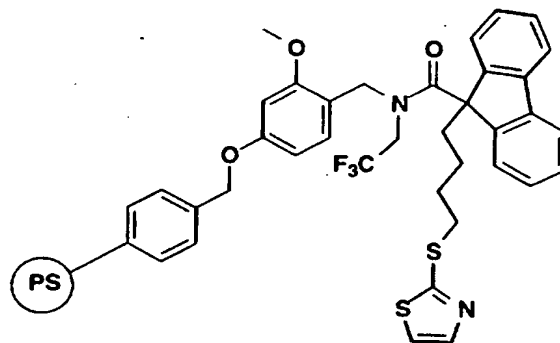
B.



To the Part A resin in the polypropylene tube were added 1 mL of diisopropylethyl amine (5.7 mmol, 10 eq) and 1 mL of CH₂Cl₂ and the resulting mixture was mixed for 2 min. The tube was cooled to 0°C in an ice bath and 4 mL (2.2 mmol, 4 eq) of a solution of Example 311 Part C acid chloride in CH₂Cl₂ was added. The resulting orange reaction mixture was mixed by vortexing at RT for 19 h. and then rinsed with CH₂Cl₂ (4 x 5 mL) to afford title resin which was used in the next step without characterization.

25

C.



The Part B resin in the sealed
 5 polypropylene tube was swollen in 5 mL of dry DMF
 and vortexed for 2 min. The solvent was removed
 with N₂ and vacuum and a solution of 644 mg (5.5
 mmol, 10 eq) of 2-mercaptothiazole in 4 mL of DMF
 was added to the resin followed by 5 mL (5 mmol, 9
 10 eq) of a 1.0 M solution of sodium
 bistrimethylsilylamide in THF. Vortexing was
 initiated and the reaction mixture was mixed for 17
 h at RT. The reaction solution was filtered away
 and the title resin was rinsed with DMF (4 x 5 mL),
 15 1:1 DMF:water (2 x 5 mL), water (1 x 5 mL), DMF (3
 x 5 mL) and dichloromethane (CH₂Cl₂) (4 x 5 mL).

D. 9-[4-(2-Thiazolylthio)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

20 The Part C resin was treated with 5 mL of
 100% trifluoroacetic acid and vortexed for 90 min.
 The reaction solution was collected, the resin was
 rinsed with CH₂Cl₂ (3 x 1 mL) and the combined
 reaction solution and rinses were concentrated. The
 25 products from 3 parallel reactions were each
 redissolved in 15 mL of CH₂Cl₂, pooled and
 reconcentrated to afford 395 mg (52% crude) of an
 off-white solid. Recrystallization from MeOH
 afforded 342 mg (45%) of title compound as a white
 30 solid.

mp 143-144°C.

MS(electrospray, pos. ions): m/z 463 (M + H).

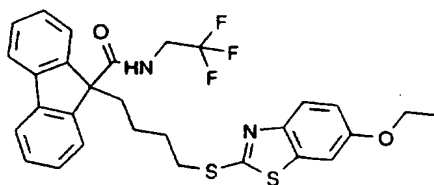
Anal. Calcd for C₂₃H₂₁N₂O₂S₂F₃:

5 C, 59.72; H, 4.58; N, 6.06; S, 13.86

Found: C, 59.65; H, 4.58; N, 6.01; S, 13.64.

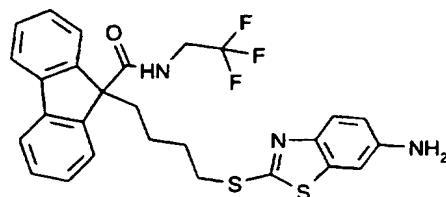
The following additional compounds were
prepared employing solid phase synthesis techniques
10 as described in Examples 311 to 313.

Example 314



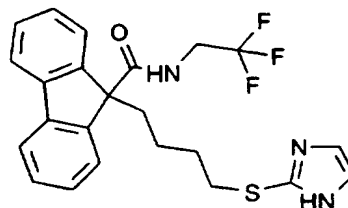
m/z 557 (M+H)

Example 315



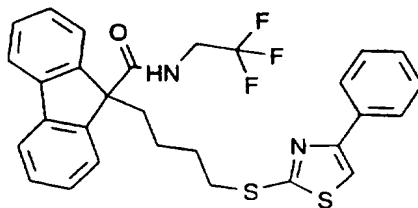
m/z 528 (M+H)

Example 316



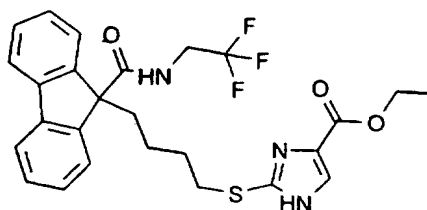
m/z 446 (M+H)

Example 317



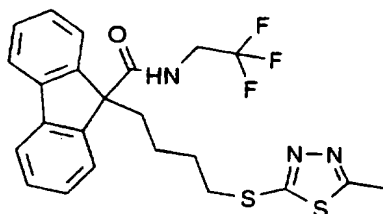
m/z 539 (M+H)

Exemple 318



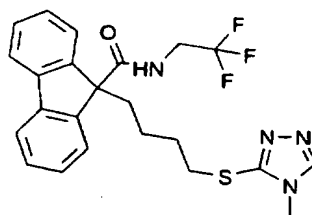
m/z 518 (M+H)

Example 319



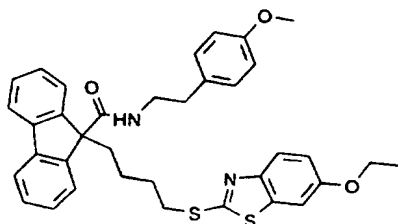
m/z 478 (M+H)

Example 320



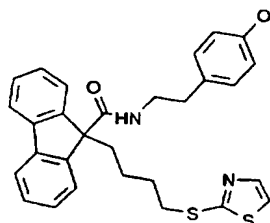
m/z 461 (M+H)

Example 321



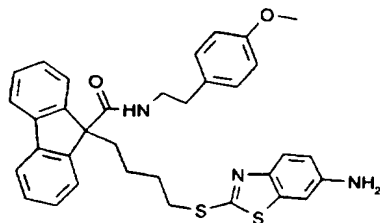
m/z 609 (M+H)

Example 322



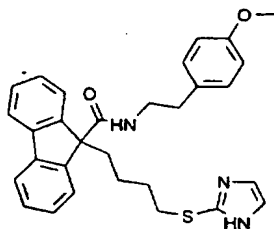
m/z 515 (M+H)

Example 323



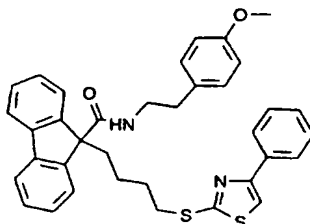
m/z 580 (M+H)

Example 324



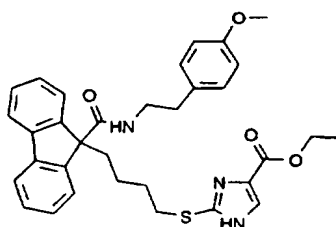
m/z 498 (M+H)

Example 325



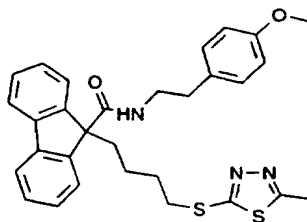
m/z 591 (M+H)

Example 326



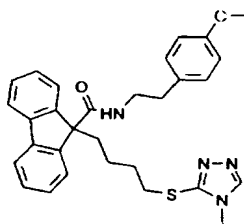
m/z 570 (M+H)

Example 327



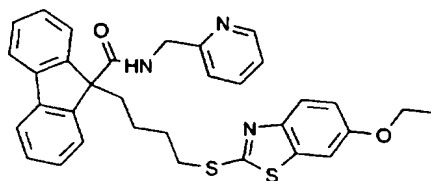
m/z 530 (M+H)

Example 328



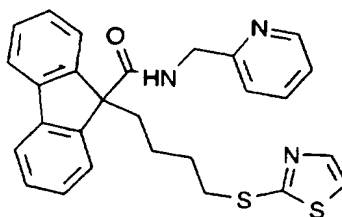
m/z 513 (M+H)

Example 329



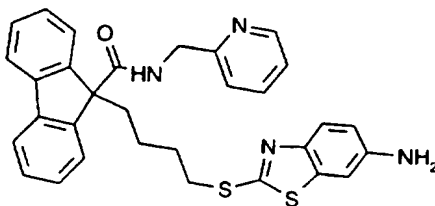
m/z 566 (M+H)

Example 330



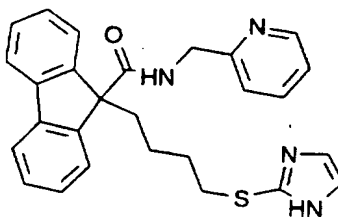
m/z 472 (M+H)

Example 331



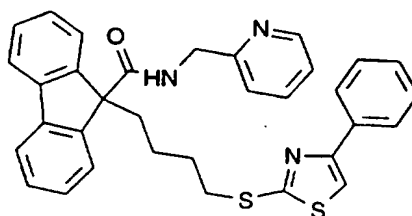
m/z 537 (M+H)

Example 332



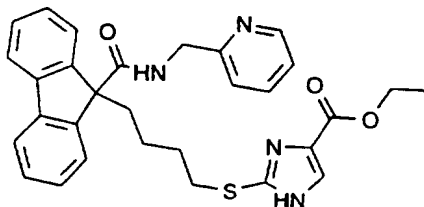
m/z 455 (M+H)

Example 333



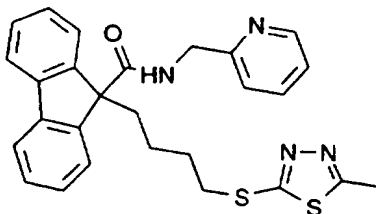
m/z 548 (M+H)

Example 334



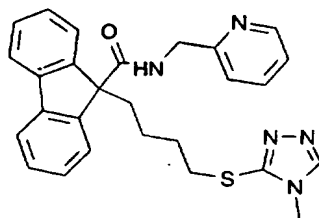
m/z 527 (M+H)

Example 335



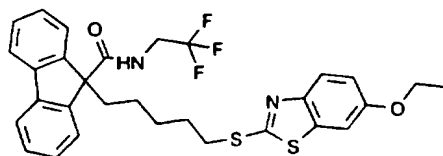
m/z 487 (M+H)

Example 336



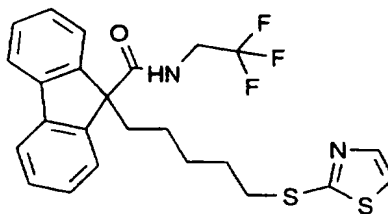
m/z 470 (M+H)

Example 337



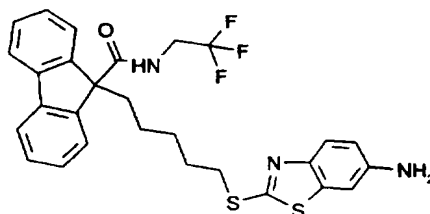
m/z 571 (M+H)

Example 338



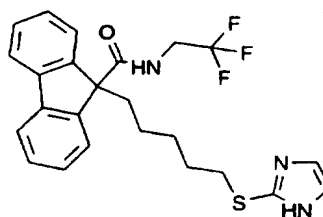
m/z 477 (M+H)

Example 339



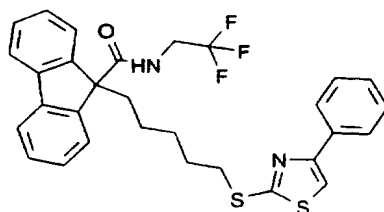
m/z 542 (M+H)

Example 340



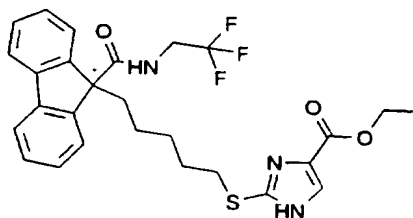
m/z 460 (M+H)

Example 341



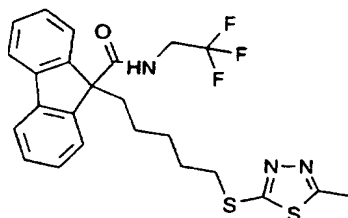
m/z 553 (M+H)

Example 342



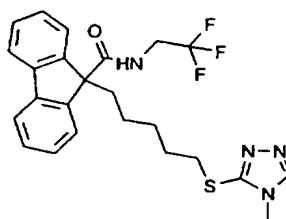
m/z 532 (M+H)

Example 343



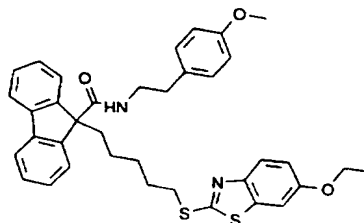
m/z 492 (M+H)

Example 344



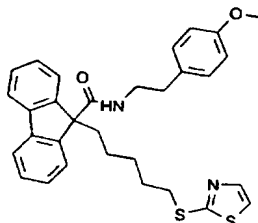
m/z 475 (M+H)

Example 345



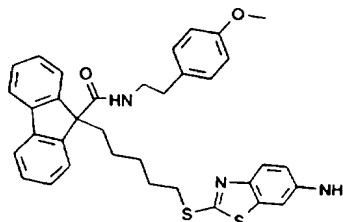
m/z 623 (M+H)

Example 346



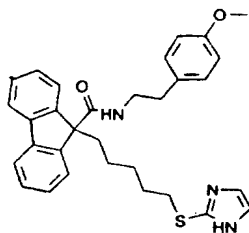
m/z 529 (M+H)

Example 347



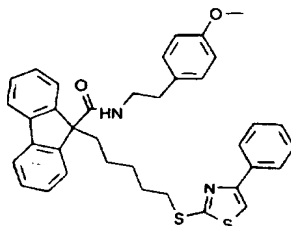
m/z 594 (M+H)

Example 348



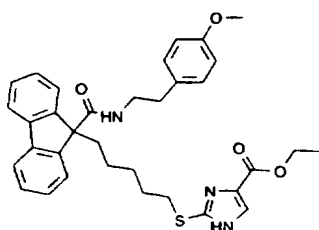
m/z 512 (M+H)

Example 349



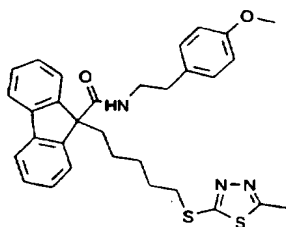
m/z 605 (M+H)

Example 350



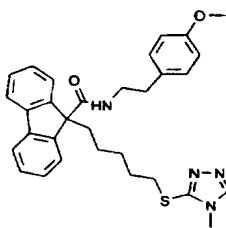
m/z 584 (M+H)

Example 351



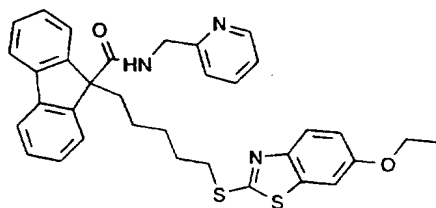
m/z 544 (M+H)

Example 352



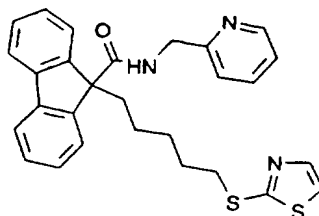
m/z 527 (M+H)

Example 353



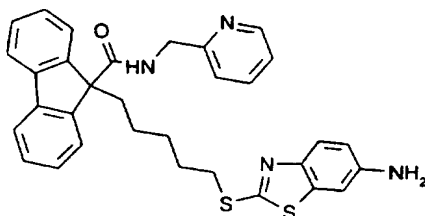
m/z 580 (M+H)

Example 354



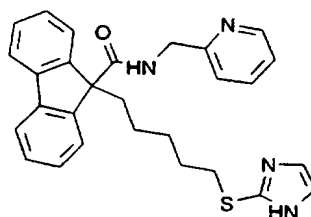
m/z 486 (M+H)

Example 355



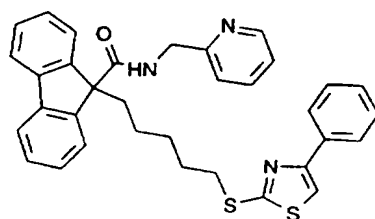
m/z 551 (M+H)

Example 356



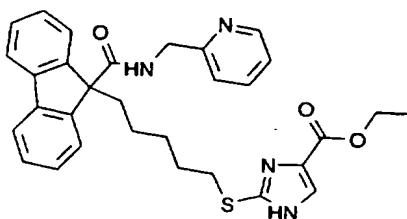
m/z 469 (M+H)

Example 357



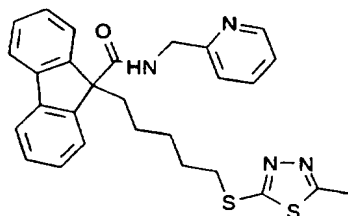
m/z 562 (M+H)

Example 358



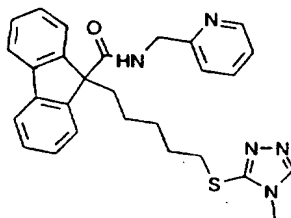
m/z 541 (M+H)

Example 359



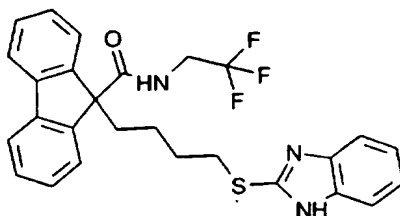
m/z 501 (M+H)

Example 360



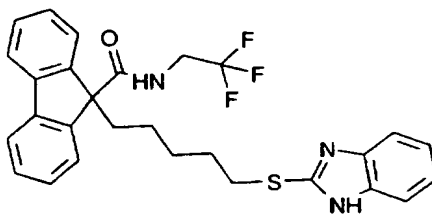
m/z 484 (M+H)

Example 361



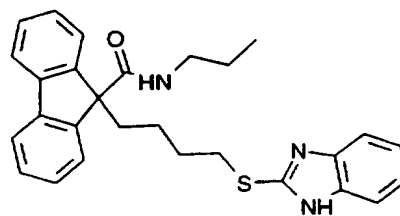
m/z 496 (M+H)

Example 362



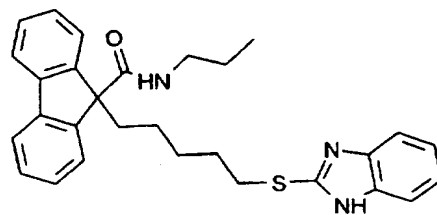
m/z 510 (M+H)

Example 363



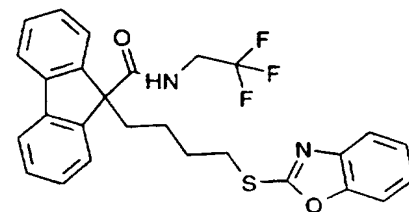
m/z 456 (M+H)

Example 364



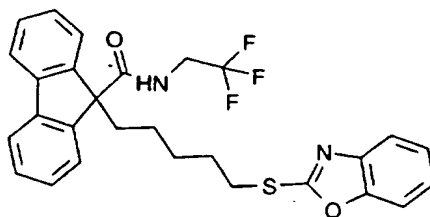
m/z 470 (M+H)

Example 365

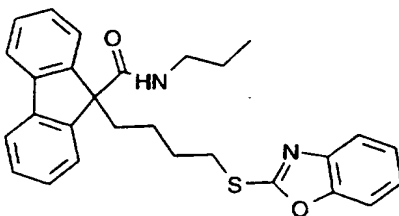


m/z 497 (M+H)

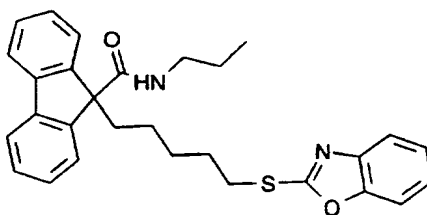
Example 366

 m/z 511 (M+H)

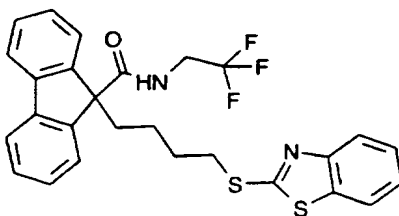
Example 367

 m/z 457 (M+H)

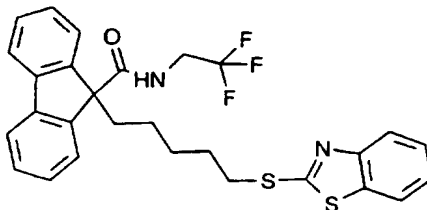
Example 368

 m/z 471 (M+H)

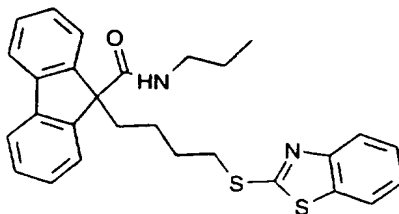
Example 369

 m/z 513 (M+H)

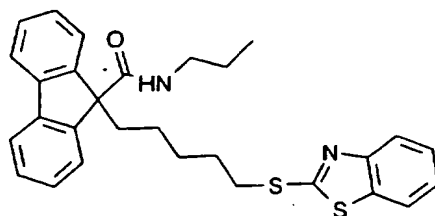
Example 370

 m/z 527 (M+H)

Example 371

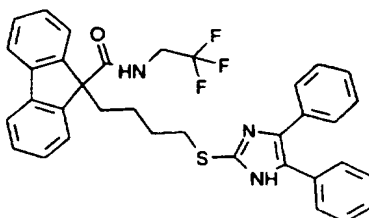
 m/z 473 (M+H)

Example 372



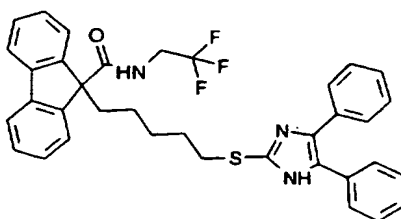
m/z 487 (M+H)

Example 373



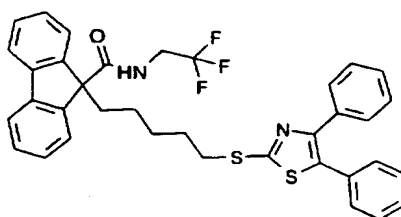
m/z 598 (M+H)

Example 374



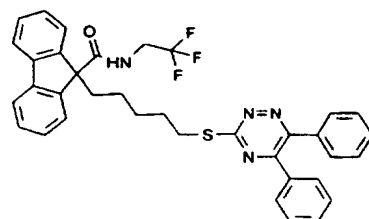
m/z 612 (M+H)

Example 375



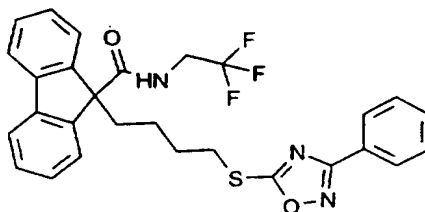
m/z 629 (M+H)

Example 376



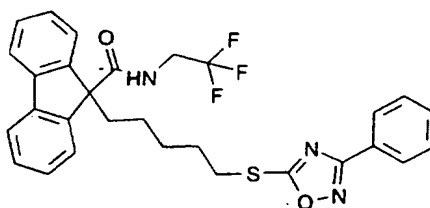
m/z 625 (M+H)

Example 377



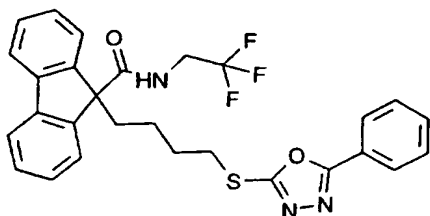
m/z 522 (M-H)

Example 378



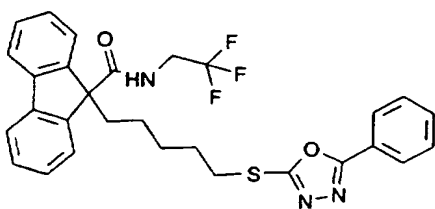
m/z 536 (M-H)

Example 379



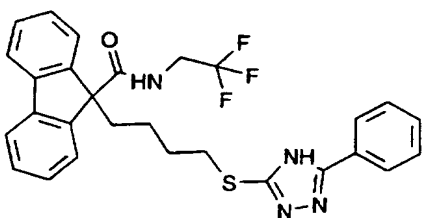
m/z 524 (M+H)

Example 380



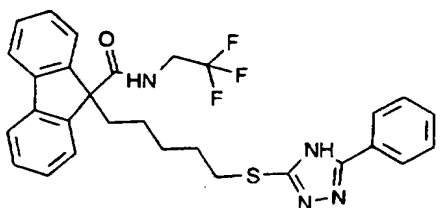
m/z 538 (M+H)

Example 381



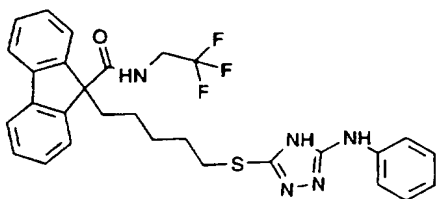
m/z 523 (M+H)

Example 382



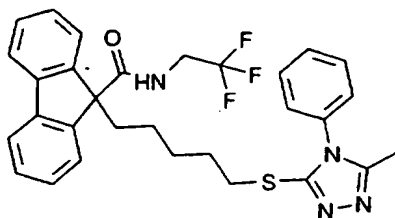
m/z 537 (M+H)

Example 383



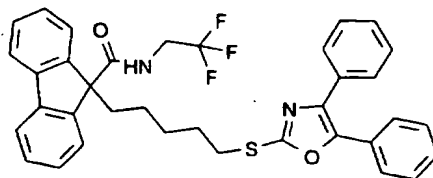
m/z 552 (M+H)

Example 384



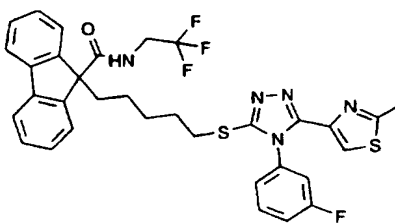
m/z 551 (M+H)

Example 385



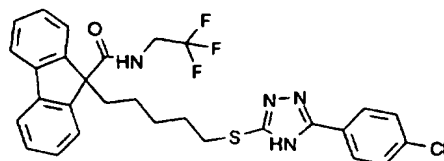
m/z 613 (M+H)

Example 386



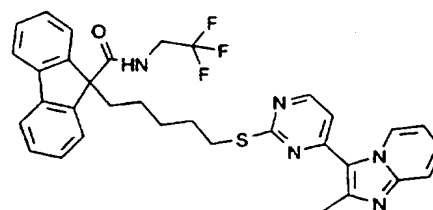
m/z 652 (M+H)

Example 387



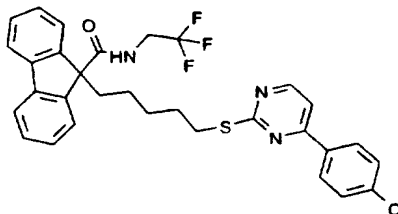
m/z 572 (M+H)

Example 388



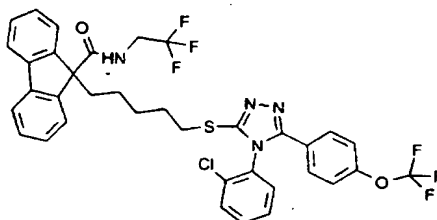
m/z 602 (M+H)

Example 389



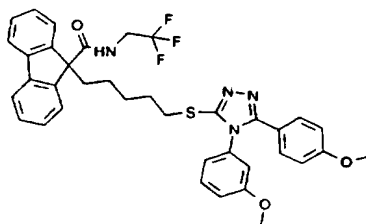
m/z 582 (M+H)

Example 390



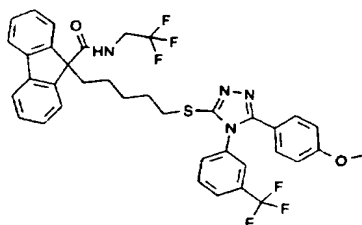
m/z 732 (M+H)

Example 391



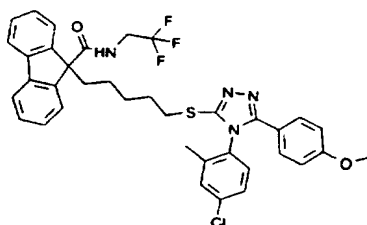
m/z 673 (M+H)

Example 392



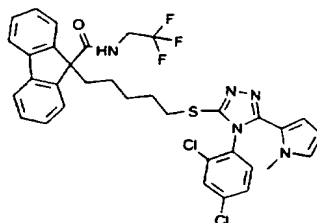
m/z 711 (M+H)

Example 393



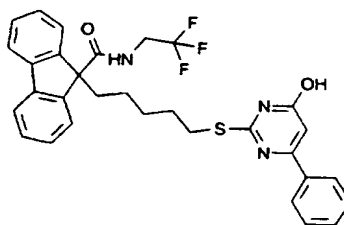
m/z 692 (M+H)

Example 394



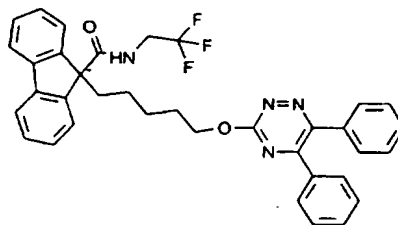
m/z 685 (M+H)

Example 395



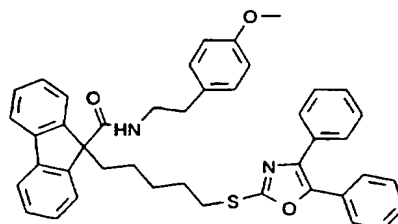
m/z 564 (M+H)

Example 396



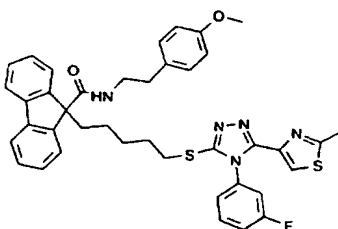
m/z 609 (M+H)

Example 397



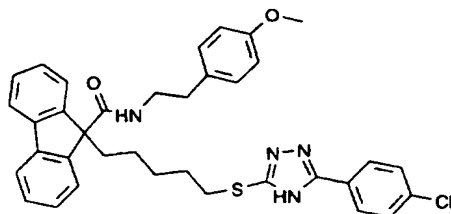
m/z 665 (M+H)

Example 398



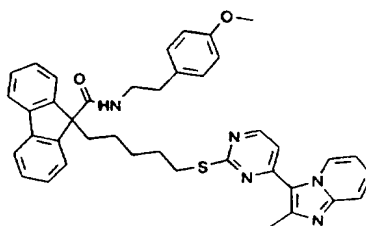
m/z 704 (M+H)

Example 399



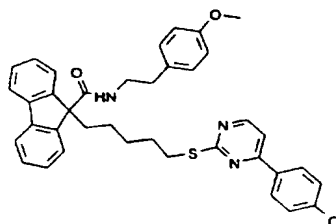
m/z 624 (M+H)

Example 400



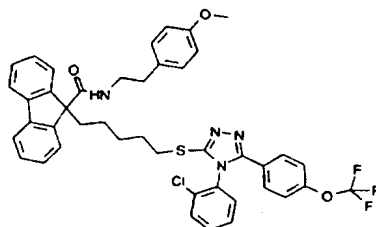
m/z 654 (M+H)

Example 401



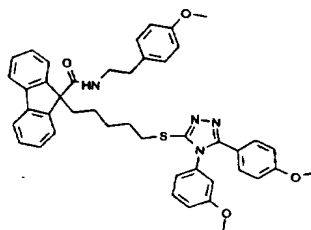
m/z 634 (M+H)

Example 402



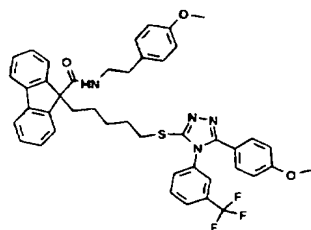
m/z 784 (M+H)

Example 403



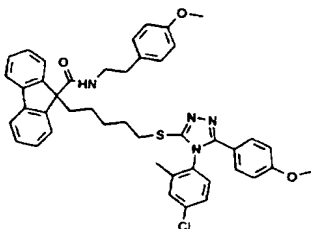
m/z 725 (M+H)

Example 404



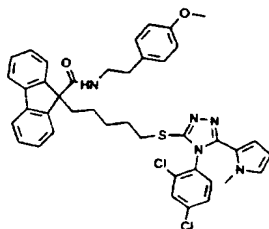
m/z 763 (M+H)

Example 405



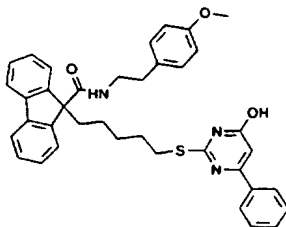
m/z 744 (M+H)

Example 406



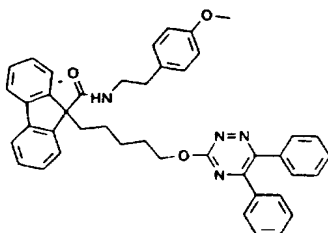
m/z 737 (M+H)

Example 407



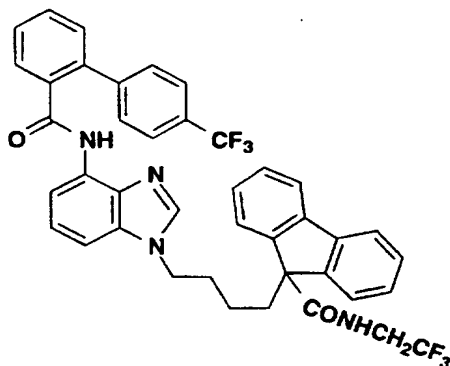
m/z 616 (M+H)

Example 408



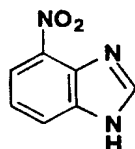
m/z 661 (M+H)

Example 409



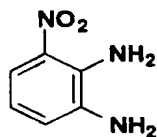
- 5 NOTE: The phrase "flash chromatography" refers to chromatography performed on EM Industries Silica Gel 60 (catalog #9385-9), 230-400 mesh under 10-20 psi of nitrogen pressure.

A.



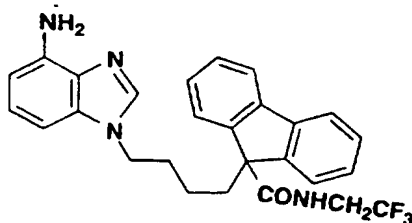
10

A stirred solution of 7.53 g (50.0 mmol) of

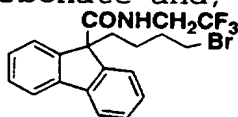


- 15 in 100 mL of 98% formic acid was set to reflux under argon for 3 hours. The reaction mixture was cooled and evaporated. The resulting solid residue was stirred with 100 mL of concentrated ammonium hydroxide for 30 min. The solids were collected, washed with 20 mL of water and dried in vacuo at 40°C to give title compound
- 20 as a white solid, 7.76 g, 95%, mp 238-240°C.

B.



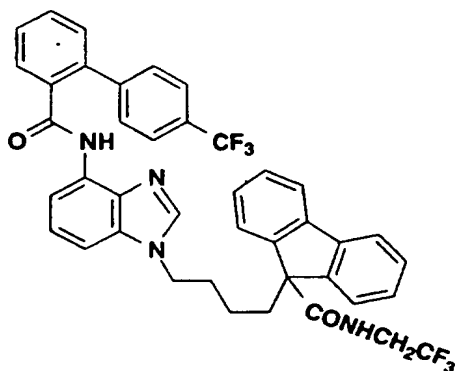
5 To a stirred solution of 2.50 g (15.0 mmol) of Part A compound in 30 mL of DMF at room temperature under argon was added 3.0 g (22 mmol) of potassium carbonate and, after 30 min, 6.80 g



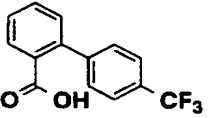
(16.0 mmol) of (prepared in Example 10 273 Part A(2)). After 24 h, the reaction mixture was quenched with 200 mL of water. The gummy solid that formed was collected, washed with water and dissolved in dichloromethane. This solution was washed twice with water, once with brine, dried 15 (MgSO₄) and evaporated. The resulting semi-solid was triturated with cold ether and collected. Without characterization, a stirred slurry of this material and 200 mg of 10% palladium-on-charcoal in 50 mL of ethanol was purged with argon and 20 evacuated three times. Hydrogen was introduced to the partially evacuated solution via a bladder. After 20 h, the reaction mixture was purged with argon, passed through a 0.45 μ nylon filter, washing with dichloromethane and evaporated. The 25 oily product was purified by flash chromatography on silica gel (5x25 cm column, 3:97 methanol/ethyl acetate) to give title compound as a white amorphous solid, 3.02 g, 42% overall yield from Part A compound.

30

C.



To a solution of 1.50 g (3.13 mmol) of Part

- 5 B compound, 835 mg (3.13 mmol) of , 425 mg of HOAt (3.13 mmol) and 220 μ L of triethylamine (1.58 mmol) in 10 mL of dichloromethane was added 680 mg (3.6 mmol) of EDAC. After 48 h, the reaction mixture was quenched with saturated sodium
- 10 bicarbonate solution and extracted twice with ethyl acetate. The extracts were combined, dried (MgSO_4) and evaporated. Purification by flash chromatography on silica gel (5x20 cm column, 8:17 hexanes/ethyl acetate) gave title compound as a
- 15 white amorphous solid, 1.43 g, 63%.

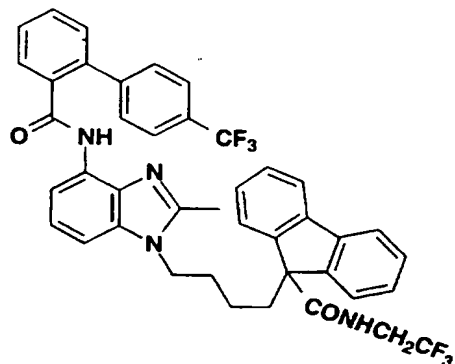
MICROANALYSIS: Calculated for $\text{C}_{41}\text{H}_{32}\text{F}_6\text{N}_4\text{O}_2 + 0.5$

EtOAc:

C, 67.01; H, 4.71; N, 7.27; F, 14.79

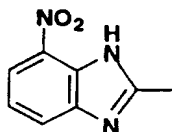
- 20 Found: C, 66.95; H, 4.36; N, 7.36; F, 14.76.

MS (electrospray, + ions) m/e 727 (M+H).

Example 410

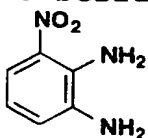
NOTE: The phrase "flash chromatography" refers to
 5 chromatography performed on EM Industries Silica
 Gel 60 (catalog #9385-9), 230-400 mesh under 10-20
 psi of nitrogen pressure.

A.



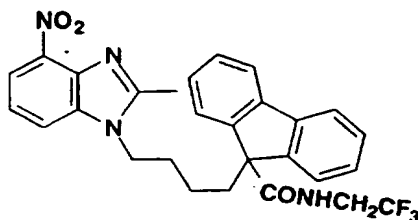
10

To a refluxing solution of 1.53 g (10.00

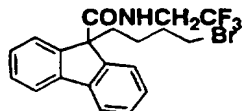


mmol) of
 5 M hydrochloric acid under argon was added 2.00 g
 (20.0 mmol) of 2,4-pentanedione over the course of
 15 5 min. After an additional 25 min at reflux, the
 reaction was cooled, neutralized with saturated
 sodium bicarbonate solution and partially
 evaporated to remove ethanol. The residual mass
 was extracted twice with ethyl acetate. The
 20 extracts were combined, dried (MgSO₄) and
 evaporated to give title compound as a tan solid,
 1.35 g, 76%, mp 215-217°C.

B.



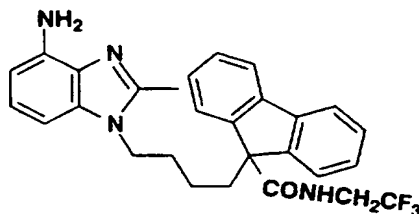
To a stirred slurry of 1.00 g of Part A
 5 compound (5.64 mmol) in 10 mL of DMF at room
 temperature under argon was added 1.00 g (7.2 mmol)
 of potassium carbonate. After 30 min, 2.55 g (6.0



mmol) of (prepared in Example 273
 Part A(2)) was added and the reaction stirred for
 10 86 h. The reaction mixture was quenched with 30 mL
 of water. The resulting solids were filtered,
 washed with water and dissolved in dichloromethane.
 The organic extract was washed with water, dried
 (MgSO_4) and evaporated onto 10 g of silica gel.
 15 Purification by flash chromatography (5x25 cm
 column, 3:7 ethyl acetate/dichloromethane) gave
 title compound as a white solid, mp 187-189°C, 2.03
 g, 69%.

20

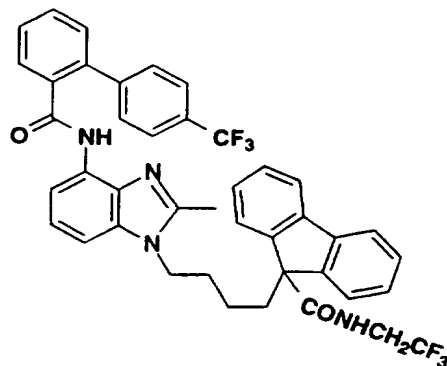
C.



A stirred slurry of 1.00 g (1.91 mmol) of
 Part B compound and 200 mg of 10% palladium-on-
 25 charcoal in 25 mL of ethanol was purged with argon
 and evacuated three times. Hydrogen was introduced
 to the partially evacuated solution via a bladder.
 After 14 h, the reaction mixture was purged with

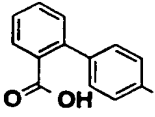
argon and passed through a 0.45 μ nylon filter, washing with dichloromethane. The filtrate was evaporated and then re-evaporated twice from dichloromethane to give title compound as a white foam. The material was used in the next reaction without purification or characterization.

D.



10

To all of Part C compound, was added 508 mg

(1.90 mmol) of , 260 mg of HOAt (1.91 mmol) and 132 μ L of triethylamine (0.95 mmol) in 10 mL of dichloromethane was added 230 mg (2.2 mmol) of EDAC. After 70 h, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted twice with dichloromethane. The extracts were combined, dried (MgSO_4) and evaporated. Purification by flash chromatography on silica gel (5x20 cm column, 1:4 ether/dichloromethane) gave title compound as a white solid, 1.10 g, 78%, mp 110-112°C.

MICROANALYSIS: Calculated for $C_{42}H_{34}F_6N_4O_2$:

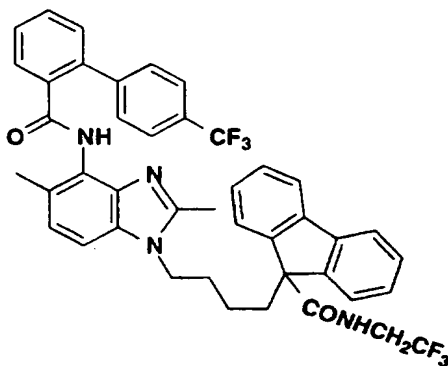
C, 68.10; H, 4.63; N, 7.56; F, 15.39

Found: C, 67.82; H, 4.69; N, 7.31; F, 15.44.

MS (electrospray, + ions) m/e 741 (M+H).

5

Example 411



Preparation of compounds Parts A, B and C were by
10 modifications of the procedures found in the
following references:

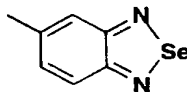
1. S. Grivas, W. Tian, E. Ronne, S. Lindström and
K. Olsson; *Acta Chem. Scand.*, 47 521 (1993);

15

2. W. Tian and S. Grivas; *Synthesis* 29 1305
(1992).

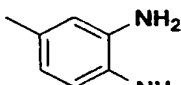
NOTE: The phrase "flash chromatography" refers to
20 chromatography performed on EM Industries Silica
Gel 60 (catalog #9385-9), 230-400 mesh under 10-20
psi of nitrogen pressure.

A.



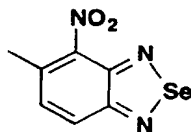
25

To a stirred solution of 48.95 g (0.400

mol) of  in 500 mL of 2.4 M hydrochloric
acid at 80°C under argon, was added a warm solution

of 88.77 g (0.800 mol) of selenium dioxide in 300 mL of water dropwise over the course of 30 min. After an additional 90 min, the reaction was cooled to room temperature and the solids were collected, washing with water. The brown solids were dried in vacuo at 50°C to give title compound, 75.10 g, 95% yield, mp 67-69°C.

B.



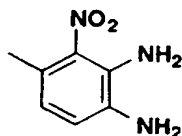
To a stirred solution of 72.00 g (0.365 mol) of Part A compound in 180 mL of 98% sulfuric acid at 10°C was added a cold solution of 108.0 mL of 2:1 98% sulfuric acid/70% nitric acid over 1 h. The temperature of the reaction mixture was not allowed to rise above 20°C. After an additional 60 min, the reaction was poured as a thin stream into 750 g of ice with rapid stirring. The fine yellow slurry was filtered and the collected solids were washed five times with 200 mL portions of cold water. The moist cake was heated in 500 mL of ethanol to near boiling and then cooled to room temperature and the solid collected. Drying in vacuo at 50°C gave title compound as a yellow solid, 80.70 g, 91% yield, mp 190-192°C.

MICROANALYSIS: Calculated for C₇H₅N₃O₂Se:

C, 34.73; H, 2.08; N, 17.36; Se, 32.61

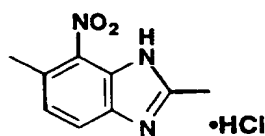
Found: C, 34.96; H, 1.97; N, 17.35; Se, 32.59.

C.



To a stirred solution of hydriodic acid (25.0 mL, 57%, 189 mmol, Aldrich catalog #21,002-1, stabilized with 1.5% hypophosphorous acid) at room temperature in argon was added 5.00 g (20.7 mmol) of Part B compound. The reaction vessel was placed in an oil bath pre-heated to 50°C and the resulting deep red solution was vigorously stirred for 2 h. After cooling to room temperature the reaction mixture was poured into a stirred slurry of 24 g (0.2 mol) of sodium hydrogen sulfite in 50 mL of water. The resulting light yellow slurry was treated with an ice-cold solution of sodium hydroxide (7.5 g, 188 mmol) in 50 mL of water. Additional 6 M sodium hydroxide was added until the aqueous slurry was brought to pH 8. The resulting deep red slurry was filtered and the filtrate extracted three times with 200 mL portions of chloroform. The solids from the filtration were dissolved in 300 mL of chloroform and washed once with 50 mL of water. The organic extracts were combined, dried (Na₂SO₄) and evaporated to give title compound as a deep red solid, 3.04 g, 88% yield, mp 132-133°C.

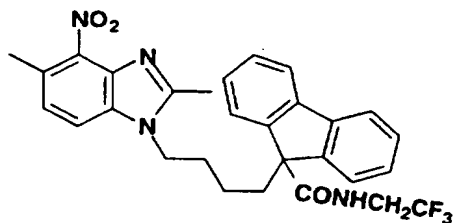
25 D.



To a refluxing solution of 1.00 g (6.00 mmol) of Part C compound in 27 mL of ethanol and 7.2 mL of 5 M hydrochloric acid under argon was added 1.20 g (12.0 mmol) of 2,4-pentanedione over the course of 5 min. After an additional 60 min at reflux, the reaction was cooled and partially evaporated to remove ethanol. The resulting precipitate was filtered, washed with water and

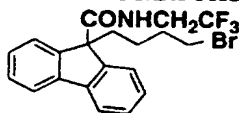
dried in vacuo at 40°C to give title compound as a tan solid, 1.12 g, 98%, mp 232-234°C.

E.



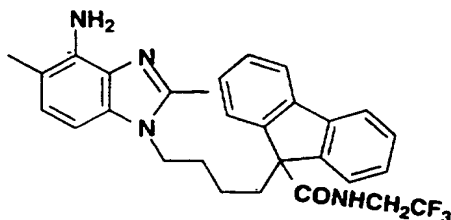
5

To a stirred slurry of 1.80 g of the free base of Part D compound (9.41 mmol) in 15 mL of DMF at room temperature under argon was added 1.75 g (33 mmol) of potassium carbonate. After 1 h, 4.26



g (10.0 mmol) of (prepared in Example 273 Part A(2)) was added and the reaction stirred for 86 h. The reaction mixture was quenched with 30 mL of water. The liquids were decanted away from the formed gummy solid, which was then washed with water. The semi-solid residue was triturated with 40 mL of ether. The resulting granular solid was chilled and filtered. The collected solid cake was washed with water, transferred to a round bottom flask and evaporated from toluene. The dried residual solid was triturated with hot ethyl acetate and filtered to give 4.02 g of title compound (80%) as a white solid, mp 181-183°C. Analytical HPLC indicated that the compound was 98.7% pure.

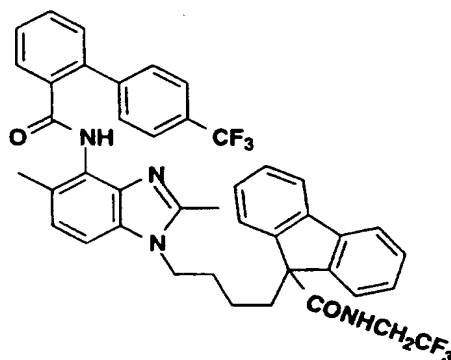
F.



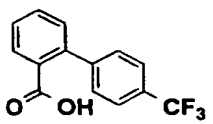
A stirred slurry of 1.05 g (1.96 mmol) of
 5 Part E compound and 200 mg of 10% palladium-on-
 charcoal in 40 mL of ethanol was purged with argon
 and evacuated three times. Hydrogen was introduced
 to the partially evacuated solution via a bladder.
 After 14 h, the reaction mixture was purged with
 10 argon and passed through a 0.45 μ nylon filter,
 washing with dichloromethane. The filtrate was
 evaporated and then re-evaporated twice from
 dichloromethane to give title compound as a white
 foam, 0.958 g, 99%.

15

G.



To a solution of 536 mg (1.00 mmol) of Part

20 F compound, 270 mg (1.02 mmol) of , 136
 mg of HOAt (1.00 mmol) and 70 μ L of triethylamine
 (0.5 mmol) in 2 mL of dichloromethane was added 230
 mg (1.2 mmol) of EDAC. After 70 h, the reaction
 mixture was quenched with saturated sodium
 25 bicarbonate solution and extracted twice with

dichloromethane. The extracts were combined, dried
(MgSO_4) and evaporated. Purification by flash
chromatography on silica gel (5x20 cm column, 1:9
hexanes/ethyl acetate) gave title compound as a
5 white amorphous solid, 440 mg, 58%.

MICROANALYSIS: Calculated for $\text{C}_{43}\text{H}_{36}\text{F}_6\text{N}_4\text{O}_2 + 1.4$
 $\text{H}_2\text{O} + 0.2 \text{ EtOAc}$:

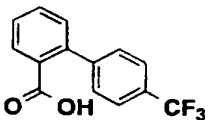
C, 65.96; H, 5.11; N, 7.02

10 Found: C, 65.95; H, 4.72; N, 7.08.

MS (electrospray, + ions) m/e 755 (M+H).

Preparation of G [ALTERNATIVE]:

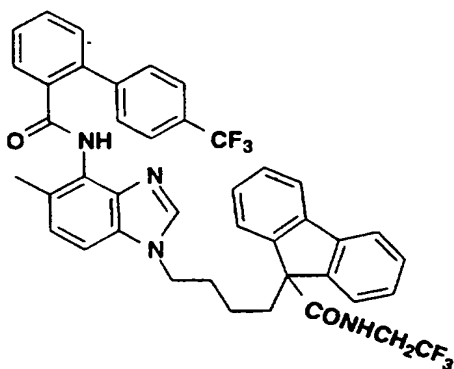
To a stirred slurry of 1.72 g (6.47 mmol)



15 of O=C(O)c1ccccc1-c2ccc(C(F)(F)F)cc2 in 15 mL of dichloromethane
(protected from atmospheric moisture by a Drierite-
filled tube) was added 0.85 mL (9.74 mmol) of
oxalyl chloride and then 0.1 mL of DMF. Gas
evolves and, within a few minutes, a colorless
20 solution formed. After 1 h, IR indicated that
complete reaction had occurred. The reaction was
evaporated twice from dichloromethane and then
rediluted with 10 mL of dichloromethane. This
solution was added dropwise to a solution of 3.21 g
25 of Part F compound and 1.00 mL (7.17 mmol) of
triethylamine at 0°C under argon. Total addition
took 20 min and then the reaction was warmed to
room temperature. After 90 min, the reaction
mixture was quenched with saturated sodium
30 bicarbonate solution and extracted twice with
dichloromethane. The extracts were combined, dried
(MgSO_4) and evaporated. Recrystallization from
ethyl acetate/hexanes provided title compound as a
white solid, mp 126-128°C, 3.86 g, 81% yield.

35

Example 412



NOTE: The phrase "flash chromatography" refers to chromatography performed on EM Industries Silica Gel 60 (catalog #9385-9), 230-400 mesh under 10-20 psi of nitrogen pressure.

A.



10

A refluxing solution of 1.586 g (9.49 mmol) of Example 411 Part C in 19 mL of 98% formic acid under argon was stirred for 90 min. The reaction mixture was cooled and evaporated. The syrupy residue was cautiously treated with 20 mL of concentrated ammonium hydroxide solution and stirred for 15 min. The resulting tan solid was collected, washed with 20 mL of cold water and dried in vacuo at 40°C to give title compound as a tan solid, 1.63 g, 97%, mp 237-239°C.

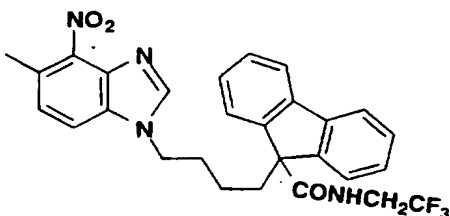
MICROANALYSIS: Calculated for $C_8H_7N_3O_2 + 0.12 H_2O$:

C, 53.58; H, 4.07; N, 23.43

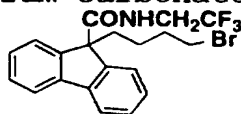
Found: C, 53.66; H, 3.88; N, 23.62.

25

B.



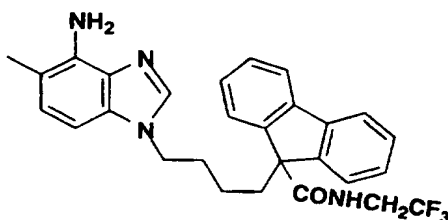
To a stirred slurry of 1.587 g of Part A
 5 compound (8.96 mmol) in 15 mL of DMF at room
 temperature under argon was added 1.50 g (10.9
 mmol) of potassium carbonate. After 1 h, 4.26 g



(10.0 mmol) of (prepared in Example
 273 Part A(2)) was added and the reaction stirred
 10 for 20 h. The reaction mixture was quenched with
 water. The liquids were decanted away from the
 formed gummy solid, which was then washed with
 water. The semi-solid residue was dissolved in
 ethyl acetate, washed twice with water, once with
 15 brine and dried (MgSO₄). Two purifications by
 flash chromatography on silica gel (5x20 cm column,
 57:43 ethyl acetate/hexanes) gave 3.05 g of title
 compound (45%) as a white amorphous solid.

20

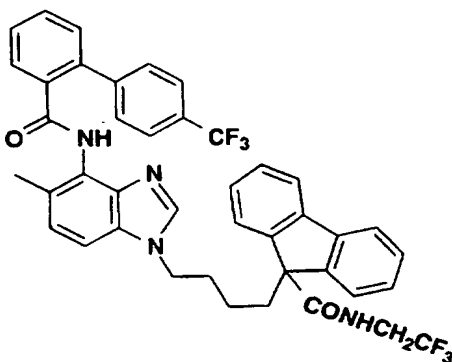
C.



A stirred slurry of 500 mg (0.96 mmol) of
 Part B compound and 200 mg of 10% palladium-on-
 25 charcoal in 20 mL of ethanol was purged with argon
 and evacuated three times. Hydrogen was introduced
 to the partially evacuated solution via a bladder.
 After 14 h, the reaction mixture was purged with

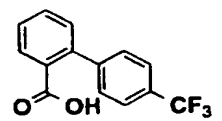
argon and passed through a 0.45 μ nylon filter,
 washing with dichloromethane. The filtrate was
 evaporated and then re-evaporated twice from
 dichloromethane to give title compound as a white
 5 foam, 0.455 g, 97%.

D.



10

To a solution of 411 mg (0.834 mmol) of



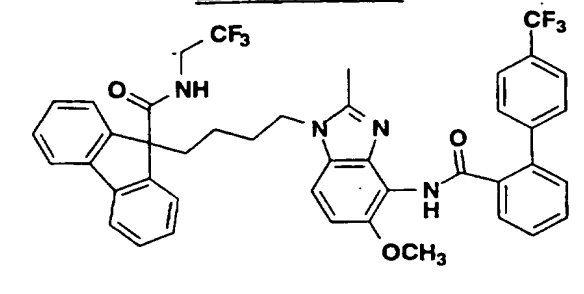
Part C compound, 222 mg (0.85 mmol) of
 114 mg of HOAt (0.838 mmol) and 58 μL of
 triethylamine (0.4 mmol) in 4 mL of dichloromethane
 was added 190 mg (1.0 mmol) of EDAC. After 66 h,
 15 the reaction mixture was quenched with saturated
 sodium bicarbonate solution and extracted twice
 with dichloromethane. The extracts were combined,
 dried (MgSO_4) and evaporated. Purification by
 flash chromatography on silica gel (5x20 cm column,
 20 2 L 1:4 hexanes/ethyl acetate, then 1:5
 hexanes/ethyl acetate) gave title compound as a
 white amorphous solid, 258 mg, 42%.

MICROANALYSIS: Calculated for $\text{C}_{42}\text{H}_{34}\text{F}_6\text{N}_4\text{O}_2 + 0.5$
 25 $\text{H}_2\text{O} + 0.5 \text{ EtOAc}$:

C, 66.58; H, 4.95; N, 7.06

Found: C, 66.63; H, 4.67; N, 7.28.

MS (electrospray, + ions) m/e 741 (M+H).

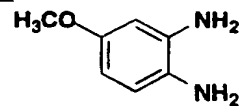
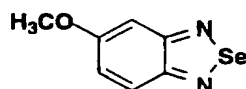
Example 413

5 Preparation of compounds of Parts A, B and C were by modifications of the procedures found in the following references:

1. S. Grivas, W. Tian, E. Ronne, S. Lindstrom and
10 K. Olsson; Acta Chem. Scand., 47 521 (1993).
2. W. Tian and S. Grivas; Synthesis 29 1305 (1992).

NOTE: The phrase "flash chromatography" refers to chromatography performed on EM Industries Silica
15 Gel 60 (catalog #9385-9), 230-400 mesh under 10-20 psi of nitrogen pressure.

A.

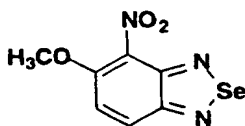


- 20 To a stirred solution of
g, 25.0 mmol) in 75.0 mL of 1 M HCl at 80°C under argon, was added a solution of selenium dioxide (5.55 g, 50.0 mmol) in 37.5 mL of water dropwise over the course of 0.5 h. Some solid was formed.
- 25 The reaction was stirred an additional 0.5 h at 80°C and then cooled to 0°C. The resulting solid was collected, washed with water, and dried in vacuum at 50°C. The filtrate was extracted with ethyl acetate (2x80 mL). The combined extracts
- 30 were washed twice with brine, dried (Na₂SO₄) and

evaporated to give additional solid. The solids were combined to provide title compound as a brown solid, 5.09 g (95.5%), mp 108-9°C.

5

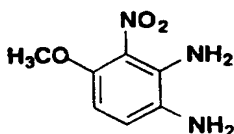
B.



To a stirred solution of Part A compound (4.70 g, 22.1 mmol) in 98% H₂SO₄ (40 mL) at 5°C was added a cold solution of 98% H₂SO₄ (8 mL) and 70% HNO₃ (4 mL), dropwise over 0.5 h. After an additional 1 h at 5°C, the reaction mixture was poured into ice (40 g). Some yellow solid was formed. The solution was neutralized to pH 10-11 by 1 N NaOH, extracted with ethyl acetate, washed twice with brine, dried (Na₂SO₄) and evaporated to give title compound, 5.25 g (92.0%) as a yellow solid (mp 234-5°C).

20

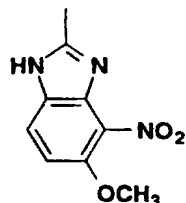
C.



To a stirred solution of Part B compound (5.10 g, 19.8 mmol) in concentrated HCl (60 mL) at room temperature under argon was added a solution of 57% HI (6 mL), dropwise over 15 minutes. After an additional 2 h, a solution of 5% NaHSO₃ (60 mL) was added and the reaction mixture was heated to 80°C for 0.5 h. After cooling to room temperature, the dark mixture was added to ethyl acetate (200 mL) and stirred for 0.5 h. The mixture was neutralized to pH 9-10 by 4 N NaOH at 5°C and filtered through Celite. The ethyl acetate layer

was washed twice with brine, dried (Na_2SO_4) and evaporated to give title compound, 2.07 g (57.1%) as a red solid (mp $114-6^\circ\text{C}$).

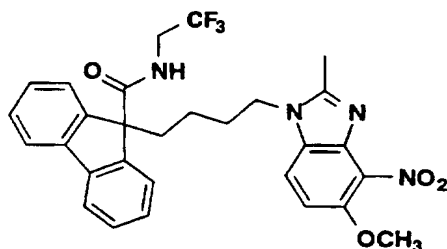
5 D.



To a stirred refluxing solution of Part C compound (1.00 g, 5.46 mmol) in 5 M HCl (6 mL) and EtOH (40 mL) under argon was added 2,4-pentanedione (1.10 g, 11.0 mmol). After refluxing 0.5 h, the reaction mixture was cooled in an ice bath and neutralized with saturated NaHCO_3 solution. The resulting yellow precipitate was filtered, washed with water and ethyl ether. The resulting solid was then dissolved in hot ethyl acetate, dried (Na_2SO_4) and evaporated to give title compound, 0.827g (73.0%) as a yellow solid (mp $200-1^\circ\text{C}$).

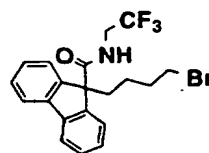
20 MICROANALYSIS: Calculated for $\text{C}_9\text{H}_9\text{N}_3\text{O}_3 + 0.36\text{Et}_2\text{O}$:
C, 53.62; H, 5.43; N, 17.97
Found: C, 54.04; H, 5.08; N, 18.35.

E.



25

A solution of Part D compound (0.800 g, 3.86 mmol) and K_2CO_3 (0.680 g, 4.94 mmol) in DMF (5 mL) under argon was stirred for 0.5 h at room



temperature. To the mixture was added
(prepared as in Example 273 Part A(2)) (1.75 g,
4.11 mmol). After 16 h, water (50 mL) was added
to the reaction mixture. The resulting yellow
5 precipitate was filtered. The solid was then
dissolved in CH₂Cl₂, washed with water, dried
(Na₂SO₄) and evaporated. The residue was purified
by flash chromatography on silica gel (5x18 cm
column, ethyl acetate) to give title compound, 1.42
10 g (66.6%) as a yellow solid (mp 87-9°C).

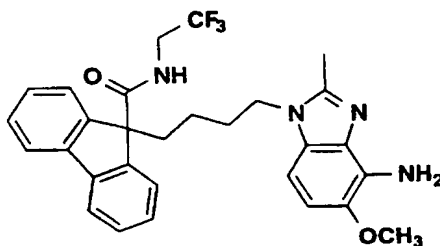
MICROANALYSIS: Calculated for

C₂₉H₂₇F₃N₄O₄+0.25AcOEt:

C, 62.71; H, 5.09; N, 9.75; F, 9.92

15 Found: C, 62.33; H, 4.86; N, 9.67; F, 10.17.

F.



20 To 10% palladium-on-charcoal (0.230 g, 9.56%
mmol) under argon was added EtOH (35 mL) and Part E
compound (1.25 g, 2.26 mmol). Hydrogen was
introduced to the solution via a bladder at room
temperature. After stirring 16 h, the reaction
25 mixture was filtered through Celite and
concentrated to give title compound, 1.09 g (92.4%)
as a light yellow solid (mp 80-1°C).

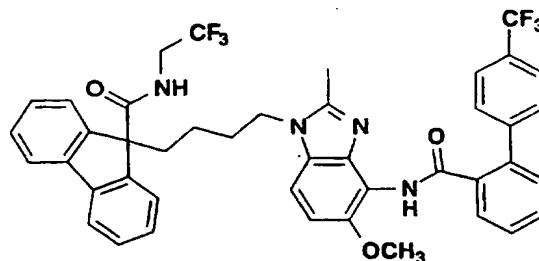
MICROANALYSIS: Calculated for $C_{29}H_{29}F_3N_4O_2 + 0.55H_2O$:

C, 65.41; H, 5.70; N, 10.52; F, 10.70

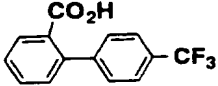
Found: C, 65.12; H, 5.56; N, 10.72; F, 11.15.

5

G.



To a solution of Part F compound (0.870 g,

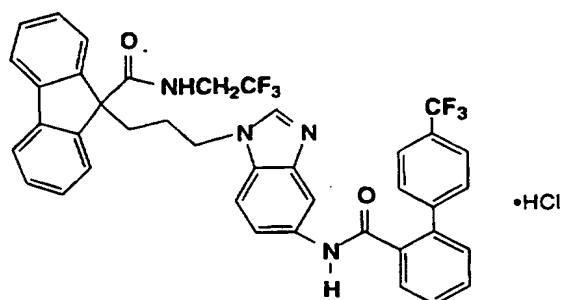
- 1.58 mmol),  (0.420 g, 1.58 mmol) and
 10 HOAt (0.240 g, 1.74 mmol) in CH_2Cl_2 (2 mL) under
 argon was added EDAC (0.330 g, 1.74 mmol) and Et_3N
 (0.080 g, 0.790 mmol). After stirring 24 h at room
 temperature, additional CH_2Cl_2 (1 mL) was added and
 stirring was continued for an additional 12 h.
 15 Saturated $NaHCO_3$ solution was added to the reaction
 mixture which was extracted with ethyl acetate,
 washed with water, dried (Na_2SO_4) and concentrated.
 The residue was purified by flash chromatography on
 silica gel (5x18 cm column, ethyl acetate followed
 20 by 1:99 methanol/ethyl acetate) to give title
 compound,
 0.512 g (42.0%) as a white amorphous solid (mp 132-
 4°C).

- 25 MICROANALYSIS: Calculated for $C_{43}H_{36}F_6N_4O_3 + 0.3$
 $AcOEt + 0.5 H_2O$:

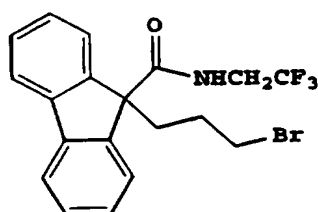
C, 65.85; H, 4.93; N, 6.95; F, 14.14

Found: C, 65.93; H, 4.69; N, 6.90; F, 14.44.

Exemple 414



A.



5

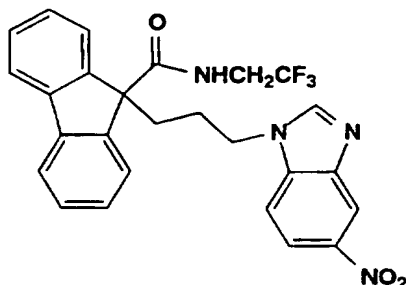
A solution of (9-fluorene)carboxylic acid (20.0 g, 92.3 mmol) in dry THF (90 ml) was placed under vacuum for 20 minutes to remove dissolved oxygen then cannulated into a cooled (0°C, ice-salt bath) solution of 1.0 M lithium t-butoxide in THF (212 ml, 2.23 eq). The ice-bath was removed and the reaction mixture stirred at room temperature for 1.0 hr. after which the green suspension was treated with 1,3-dibromopropane (18.5 ml, 1.96 eq) via syringe. The dark mixture was stirred at room temperature for 19 hours then partitioned between 30% Heptane in EtOAc (300 ml) and H₂O (250 ml), re-extracting the aqueous phase with H₂O (3 x 70 ml). The combined aqueous extracts were acidified with 2.0 N HCl to pH 2.0, extracted with CH₂Cl₂ (4 x 190 ml) and the combined CH₂Cl₂ extracts were dried (anhydrous MgSO₄), filtered, evaporated to dryness and dried in vacuo to give the crude acid as a syrup (32 g).

The acid was dissolved in dry CH_2Cl_2 (190 ml), cooled to 0°C (ice-salt bath), treated with dry DMF (0.32 ml, 0.4 eq) and $(\text{COCl})_2$ (8.2 ml, 94

mmoles), stirred at 0°C for 5 minutes then at room temperature for 2.0 hours. Meanwhile, trifluoroethylamine hydrochloride (13.8 g, 102 mmoles) was dissolved in dry CH₂Cl₂ (225 ml), cooled to 0°C (ice-salt bath), treated with Et₃N (51.5 ml) and stirred for 10 minutes. The acid mixture was cannulated into the amine solution, and stirred at 0°C, allowing the reaction mixture to come to room temperature overnight. The reaction mixture was washed sequentially with H₂O (2 x 190 ml), 1.0 N HCl (320 ml), H₂O (190 ml) and saturated NaHCO₃ (190 ml), dried (anhydrous MgSO₄), filtered, evaporated to dryness and dried in vacuo. The crude product mixture was chromatographed on a silica gel column (Merck, 4" x 13"), eluting the column with EtOAc:Hexane (1:4) to give title compound as a solid foam (22 g, 57.8 %). R_f 0.38 (Silica gel; EtOAc:Hexane-1:4; UV, PMA); m.p. 106-108°C.

20

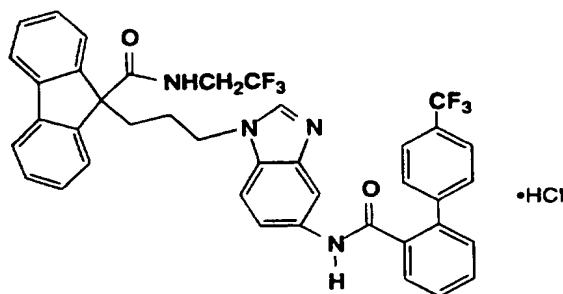
B.



A mixture of Part A compound (2.0 g, 4.85 mmoles), 5-nitrobenzimidazole (870 mg, 5.33 mmoles), and anhydrous K₂CO₃ (737 mg, 5.34 mmoles) in dry DMF (7.0 ml) was stirred at room temperature for 3 days then concentrated in vacuo. The residual syrup was partitioned between EtOAc (2 x 50 ml) and H₂O (13 ml), and the combined organic extracts were washed with H₂O (3 x 13 ml) and brine (13 ml), dried (anhydrous Na₂SO₄), filtered,

- evaporated to dryness and dried in vacuo. The crude product mixture was triturated with hot CH₃CN (2 x 25 ml), and filtered while hot to give a white solid (584 mg). The crude filtrate was
- 5 concentrated to a solid mixture and chromatographed twice on a silica gel column (Merck, 200 g), eluting each column with CH₂Cl₂:EtOAc (3:1-4.0 L) to give diastereomerically enriched title compound (1.197 g, 50.3 %, m.p. 207-8°C).
- 10 TLC : R_f 0.37 (Silica gel; EtOAc:CH₂Cl₂-6:4; UV).

C.



- 15 A solution of Part B compound (200 mg, 0.4 mmole) in dry CH₃OH (10 ml) was treated with 10 % Pd/C (40 mg) and hydrogenated (balloon) at room temperature for 20 hours. The reaction mixture was diluted with CH₃OH (10 ml) and filtered through a
- 20 celite pad in a millipore unit, washing the pad well with CH₃OH (3 x 10 ml). The combined filtrates were evaporated to dryness and dried in vacuo to give the crude amine as a syrup (196 mg).
- The amine was dissolved in dry CH₂Cl₂ (5.0
- 25 ml), treated with the 4'-(trifluoromethyl)-2-biphenylcarboxylic acid (110 mg, 0.42 mmole), HOBT·H₂O (57 mg, 0.42 mmole) and EDAC (88 mg, 0.46 mmole) and stirred at room temperature for 20
- 30 hours. The reaction mixture was partitioned between EtOAc (2 x 15 ml) and saturated NaHCO₃ (3.0 ml) and the combined organic extracts were washed with H₂O (3 x 3.0 ml) and brine (3.0 ml), dried

(anhydrous Na_2SO_4), filtered, evaporated to dryness and dried in vacuo. The crude product mixture was chromatographed on a silica gel column (Merck, 70 g), eluting the column with EtOAc:Hexane (1:2),
5 EtOAc and CH_2Cl_2 :MeOH (100:3) to give the clean free base (207 mg).

This adduct (207 mg) was dissolved in dry dioxane (2.6 ml), treated with 4.0 M HCl/dioxane (0.21 ml, 2.83 eq), swirled for a few minutes then
10 diluted with dry Et_2O (35 ml), scratching the solids as they formed. The supernatant was decanted and the solids washed with dry Et_2O (2 x 15 ml) to give title compound as a solid (163.8 mg, 53.6 %; m.p. 155-165°C, shrinking commencing at
15 150°C)).

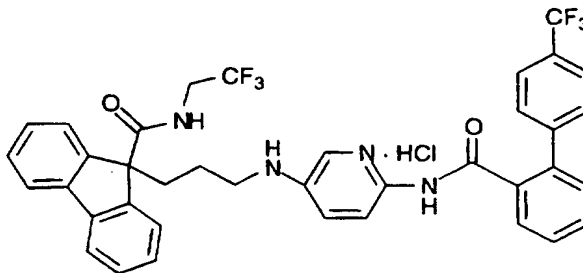
Anal. Calc'd for $\text{C}_{40}\text{H}_{30}\text{F}_6\text{N}_4\text{O}_2 \cdot \text{HCl} \cdot 0.8 \text{ H}_2\text{O}$ (Eff. Mol. Wt.=763.57):

C, 62.92; H, 4.30; N, 7.34;

20 Found: C, 62.93; H, 4.37; N, 7.11.

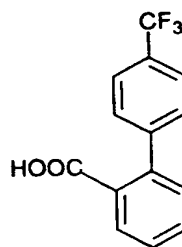
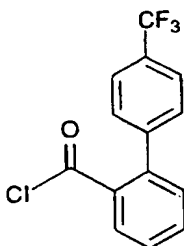
Example 415

N-(2,2,2-Trifluoroethyl)-9-[3-[[[2-[[[4'-(3,3,3-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-5-pyridinyl]amino]propyl]-9H-fluorene-9-carboxamide, monohydrochloride.



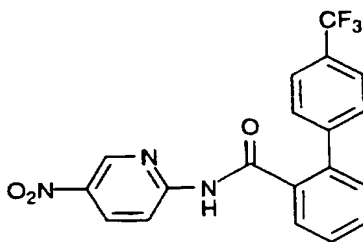
25

A.

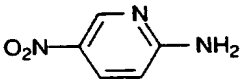


To a stirred solution of (5.32 g., 20 mmol) in 40 mL of dry CH₂Cl₂ and 40 mL of DMF at room temperature under nitrogen was slowly added 15.0 mL of 2 M oxalyl chloride in CH₂Cl₂ (30 mmol). The reaction was stirred at room temperature for 2 h and concentrated to an oil, which was dried in vacuo for 2 h and then stored at -40°C overnight to give crude title compound as an amorphous solid.

B.



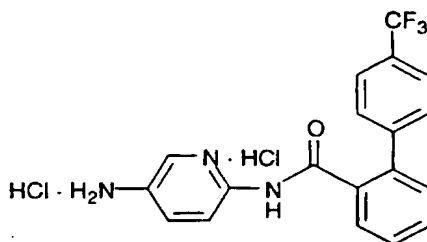
15

A mixture of 3.41 g (12 mmol) of Part A compound, 1.25 g (9 mmol) of , and 2.9 mL (36 mmol) of dry pyridine in 15 mL of dry THF was stirred at room temperature under argon for 20 h and filtered. Evaporation of the filtrate gave a residue which was taken up in CH₂Cl₂, water, and 10% Na₂CO₃. The CH₂Cl₂ was washed with dilute

Na_2CO_3 (2x) and water (2x), dried (Na_2SO_4), and concentrated to a yellow gummy residue (4.72 g). Chromatography of this residue over 450 g of silica gel using CHCl_3 , concentration, and then

5 concentration from EtOAc afforded 2.63 g (57%) of title compound as a white solid.

C.

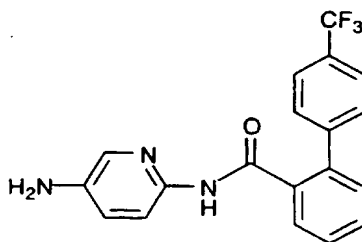


10

Part B compound (2.45 g, 6.33 mmol) was hydrogenated at 1 atmosphere with 350 mg of 10% Pd/C in 60 mL of glacial AcOH for 1.5 h. Concentrated HCl (1.1 mL, 13 mmol) was added, the mixture was filtered, and the filtrate was concentrated to a residual oil. Concentration of the oil from 95% EtOH and trituration of the oily residue from Et₂O gave 2.41 g (89%) of title compound as a solid.

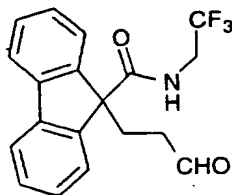
20

D.



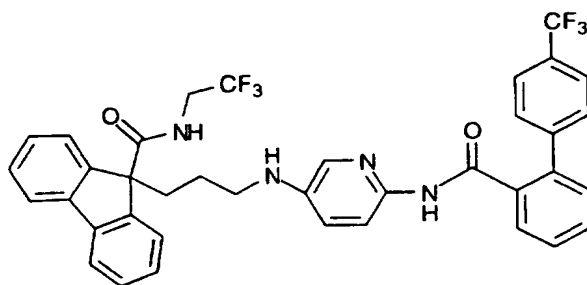
Part C compound (430 mg, 1 mmol) was shaken with CH_2Cl_2 and 5% NaHCO_3 . The CH_2Cl_2 extract was washed with 5% NaHCO_3 (2x) and then water (2x), dried (Na_2SO_4), and concentrated to give 342 mg (96%) of title compound as a yellow foam.

D(1).



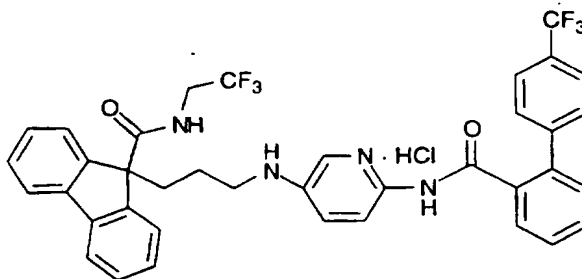
The Part D(1) compound is prepared as
5 described in Example 296 Part A.

E.



10 A mixture of Part D compound (342 mg, 0.96 mmol), Part D(1) compound (335 mg, 0.96 mmol),
glacial AcOH (0.33 mL, 5.8 mmol) and NaBH(OAc)₃ (610 mg, 2.88 mmol) in 6 mL of 1,2-dichloroethane
was stirred at room temperature under argon for 17
15 h. The mixture was diluted with CH₂Cl₂ and the organics were washed with 5% NaHCO₃ (3x) and then
water (2x), dried (Na₂SO₄) and concentrated to a foamy residue (772 mg). Chromatography of this
residue over 70 g of silica gel packed in CH₂Cl₂-
20 EtOAc (85:15) by eluting with this solvent and then CH₂Cl₂-EtOAc (80:20) afforded 329 mg (50%) of title
compound as a residue.

F.



To a solution of Part E compound (320 mg,
 5 0.46 mmol) in 4 mL of dry THF was added 0.5 mL of 4
 N HCl in dioxane and then Et₂O. The precipitate
 was collected, washed with Et₂O, and dried in vacuo
 at 40°C for 1 h to give 251 mg (75%) of title
 compound as a pale yellow solid having mp 128-
 10 132°C.

Anal. Calcd for C₃₈H₃₀F₆N₄O₂ + HCl + 0.75 H₂O + 0.15
 Et₂O:

C, 61.84; H, 4.57; N, 7.47; Cl, 4.73;
 15 F, 15.20
 Found: C, 61.91; H, 4.41; N, 7.40; Cl, 4.81;
 F, 15.48.

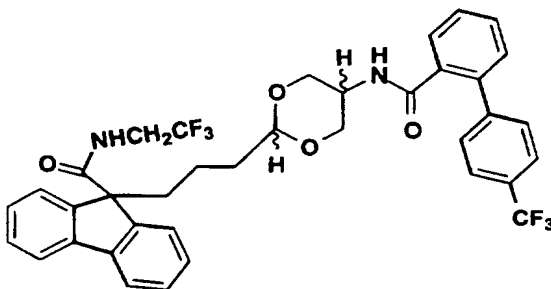
MS (ESI-NH₃, + ions) 689 (M+H); (- ions) 687 (M-H).

TLC (silica gel): R_f=0.50, CH₂Cl₂: CH₃OH (19:1).

20

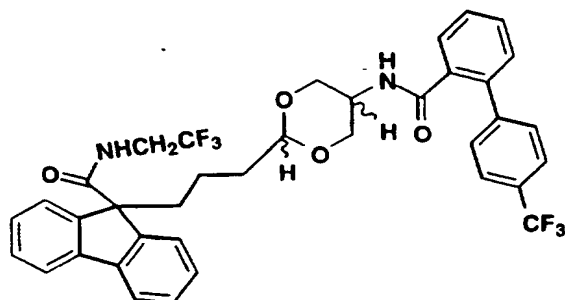
Example 416

N-(2,2,2-Trifluoroethyl)-9-[3-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-
 yl]carbonyl]amino]-1,3-dioxan-2-yl]propyl]-9H-fluorene-9-carboxamide



Isomer A

25

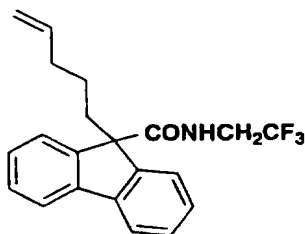
Example 416A

Isomer B

- 5 NOTE: The phrase "flash chromatography" refers to chromatography performed on EM Industries Silica Gel 60, 230-400 mesh under 10-20 psi of nitrogen pressure.

10

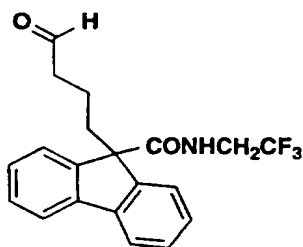
A.



- 15 A solution of 9H-fluorene carboxylic acid (5.00 g, 23.7 mmol) in 24 mL of THF at -12°C was purged and evacuated with argon three times. The solution was added via canula to an argon-purged solution of 50 mL of lithium t-butoxide (1 M in THF, 50.0 mmol) at -12°C over 5 min. After 1 h, the solution was warmed to room temperature and
- 20 $\text{Br}(\text{CH}_2)_3\text{CH}=\text{CH}_2$ (5.6 mL, 48 mmol) was added in a steady stream. After 70 h, the reaction was quenched with 1 M hydrochloric acid and extracted twice with ethyl acetate. The organic extracts were combined, dried (MgSO_4) and evaporated.
- 25 The white solid was stirred and slurried in 25 mL of dichloromethane at room temperature while oxalyl chloride (3.5 mL, 40 mmol) and DMF (0.2 mL) were added. After 1 h, the yellow solution was

evaporated twice from dichloromethane and redissolved in 20 mL of dichloromethane. This solution was added to a stirred solution of 1,1,1-trifluoroethylammonium chloride (4.10 g, 30.0 mmol) and Et₃N (12.5 mL, 89.7 mmol) in 30 mL of dichloromethane at 0°C under argon. After 1 h, the reaction was quenched with 10% citric acid solution. The organic extract was dried (MgSO₄) and evaporated. Purification by flash chromatography on silica gel (5x20 cm column, 1:1 hexane/dichloromethane) gave, after trituration in hexane, title compound, 5.40 g, 63% yield, as a white solid, mp 47-49°C.

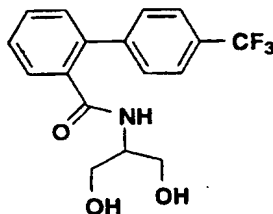
15 B.



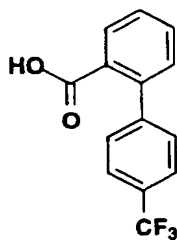
A solution of Part A compound (3.59 g, 10.0 mmol) in 100 mL of dichloromethane, protected by a Drierite-filled tube, at -78°C was treated with a stream of ozone/oxygen generated from a Welsbach Ozonizer for 20 min until a blue color persisted. Solid triphenylphosphine (2.70 g, 10.1 mmol) was added and the reaction was warmed to room temperature. After 24 h, the reaction mixture was partially evaporated and purified by flash chromatography on silica gel (5 x 20 cm column, 3:197 ether/dichloromethane) to give title compound as a low-melting solid, 3.40 g, 94%.

30

C.

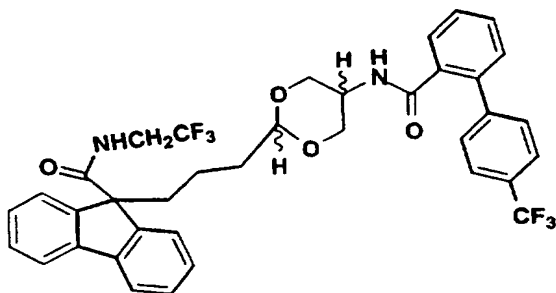


To a stirred solution of 1.33 g (5.00 mmol)



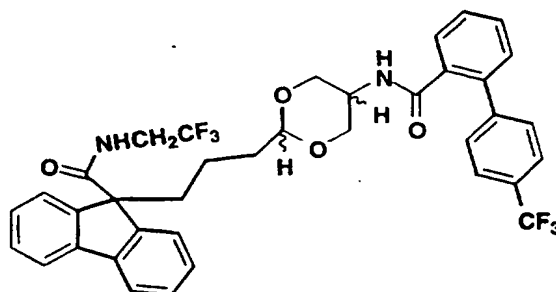
5 of CF_3 , 0.455 g (5.00 mmol) of $\begin{matrix} \text{OH} \\ \text{NH}_2 \\ \text{OH} \end{matrix}$, 0.750 g (5.0 mmol) of HOBt and 0.5 mL (3.6 mmol) of triethylamine in 10 mL of dichloromethane at room temperature under argon, was added 1.0 g (5.25 mmol) of EDAC, portion-wise, over 3 min. After 16 h, the reaction mixture was diluted with ethyl acetate, washed once with saturated sodium bicarbonate solution, once with brine and once with 10% citric acid solution, dried (MgSO_4) and evaporated. Purification by flash chromatography on silica gel (5 x 15 cm column, ethyl acetate) provided title compound as a white solid, mp 146-148°C, 1.23 g, 72% yield.

D.



Isomer A

E.



Isomer B

5 To a stirred slurry of Part C compound (340
mg, 1.00 mmol) and Part B compound (362 mg, 1.00
mmol) in 2 mL of dichloromethane at room
temperature under argon was added 98% methane-
sulfonic acid (10 μ L, 0.15 mmol). After 14 h, the
10 resulting colorless solution was quenched with
saturated sodium bicarbonate solution and extracted
twice with dichloromethane. The organic extracts
were combined, dried (Na_2SO_4) and evaporated. The
oily residue was partially purified by flash
15 chromatography on silica gel (5 x 25 cm column, 1:1
EtOAc/hexanes) to give two fractions:

Isomer A (Example 416)

80 mg, 12% yield.

20 TLC: R_f = 0.46 (3:2 EtOAc/hexane on Silica Gel
60).

Melting point: 210-212°C.

Isomer B (Example 416A)

25 420 mg, 62% yield.

TLC: R_f = 0.37 (3:2 EtOAc/hexane on Silica Gel
60).

Melting point: 85-88°C.

Mass Spectrometry: (electrospray, + ions)

30 m/z 700 ($\text{M}+\text{NH}_4^+$), 683 ($\text{M}+\text{H}$).

MICROAnal. Calcd for $C_{37}H_{33}F_6N_2O_5P$:

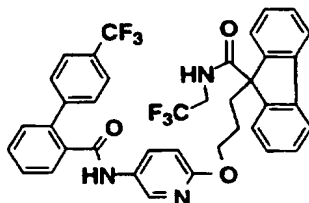
C, 65.10; H, 4.73; N, 4.10; F, 16.70

Found: C, 65.19; H, 4.91; N, 3.86; F, 16.52.

5

Example 417

N-(2,2,2-Trifluoroethyl)-9-[3-[[[5'-[[[4'-(trifluoromethyl)](1,1'-biphenyl)-2-yl]carbonyl]amino]-2-pyridinyl]oxy]propyl]-9H-fluorene-9-carboxamide, trifluoroacetate.

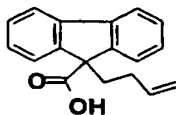


A.



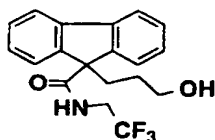
10

To a solution of the 9H-fluorene carboxylic acid (8.0 g, 38 mmol) in THF at 0°C (150 ml) was added a 1 M solution of lithium tert-butoxide (76 ml, 76 mmol) in THF. Following the addition of base, the reaction mixture was stirred vigorously at RT for 2h. The reaction mixture was treated with 1-bromo-3-butene (8.00 g, 60 mmol) and stirred overnight. TLC indicated a trace of starting acid was still present. The reaction mixture was treated with an additional 5 mL (5 mmol) of lithium tert-butoxide and the mixture stirred overnight. The mixture was quenched with NH_4Cl solution and the pH adjusted to 2 with $KHSO_4$ solution. The mixture was diluted with ethyl acetate (400 mL) and washed with water. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give an off-white foam which was partially purified by trituration with hexane to give a white solid (9.5 g) of the structure



To a solution of the above crude acid (9.5 g, 36 mmol) in dichloromethane (200 mL) was added a 2 M solution of oxalyl chloride (23 mL, 46 mmol) in dichloromethane followed by a 2 drops of DMF. The reaction (bubbled vigorously) was stirred under argon at RT for 2 h. The solvent was evaporated in vacuo and the residue was dissolved in THF (150 mL). The mixture was treated with CF₃CH₂NH₂ HCl salt (5.4 g, 40 mmol) and triethylamine (8.00 g, 78 mmol) and stirred at RT for 6 h. The reaction mass was diluted with ethyl acetate (300 mL) and washed 1N HCl and saturated K₂CO₃ solution. The organic layer was dried (MgSO₄), and the solvent was removed in vacuo to give an off-white solid which was purified by recrystallization from methanol to give 4.5 g of title compound as a white solid. The filtrate was concentrated and the residue purified by flash column chromatography to give an additional 3.5 g of title compound as a white solid (overall yield 8.0 g, 64%).

B.



25

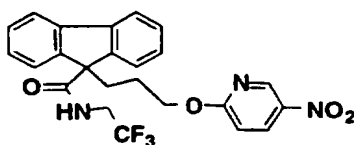
A solution of Part A compound (3.00 g, 8.7 mmol) in a mixture of 50 mL 1:1 dichloromethane/methanol at -78° C was treated with a stream of ozone in oxygen for 35 min. The mixture turned light gray and TLC indicated that the starting olefin was consumed. The reaction mixture was treated with NaBH₄ pellets (1.03 g, 27 mmol) and stirred overnight at RT. The mixture was quenched

with 50 mL of NH_4Cl solution and 150 mL ethyl acetate. The layers were equilibrated and separated. The organic fraction was dried (MgSO_4) and concentrated. The residue was purified by
5 flash column chromatography on silica gel with 1:1 ethyl acetate/hexanes to give 2.6 g (85%) of title compound as a white solid.

mp: 112-114°C

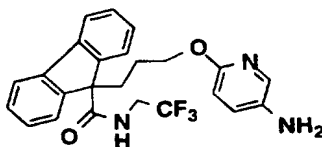
10

C.



A solution of Part B compound (2.50 g, 7.16
15 mmol) in THF was treated with NaH (192 mg, 8 mmol) at 0°C. After 1 h the alkoxide was treated with 1.30 g (8 mmol) of 2-bromo-5-nitropyridine. The mixture was stirred at RT overnight and an additional 36 mg (1.5 mmol) of NaH was added.
20 After stirring for an additional 4 hours the reaction mixture was quenched with NaHCO_3 solution and extracted with ethyl acetate. The organic fraction was dried (MgSO_4) and concentrated. The residue was purified by flash column chromatography
25 on silica gel with 6:12:1 ethyl acetate/hexanes/dichloromethane to give 3.12 g (92%) of title compound as a white solid.

D.

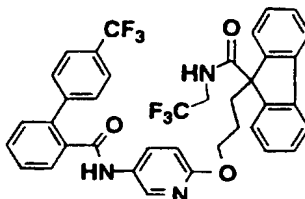


30

A solution of Part C compound (3.00 g, 6.4 mmol) in ethyl acetate (50 mL) was treated with 200

mg of 10% Pd/carbon and placed under an atmosphere of H₂ (balloon pressure). After stirring overnight the mixture was filtered through a pad of celite and the filtrate concentrated to title compound in
5 the form of a thick oil (3.00 g, ≈ 100%).

E.



10 The crude Part D amine (3.0 g, 6.3 mmol) was stripped from toluene (2 X 20 mL) and pumped to ensure complete drying. The amine was diluted with 100 mL of THF and cooled to 0°C. The solution was treated with the Example 415 Part A acid chloride
15 (1.75 g, 6.1 mmol) in 10 mL of dichloromethane. The mixture was then treated with triethylamine (0.64 g, 6.3 mmol) and a slurry resulted. The thick mixture was stirred for 1 hour at RT and diluted with 50 mL NaHCO₃ solution and 100 mL of
20 ethyl acetate. The layers were equilibrated and separated. The organic fraction was dried (MgSO₄), concentrated and purified by flash column chromatography on silica gel with 3:7 ethyl acetate/hexanes followed by 1:1 ethyl acetate/
25 hexanes to give 4.00 g (92%) of title compound as an off white solid.

mp: 115-120°C

TLC Silica gel (3:7 ethyl acetate/hexane) R_f=0.50.

30 Mass Spec. (ES-NH₃, + ions) m/z 690 (M+H).

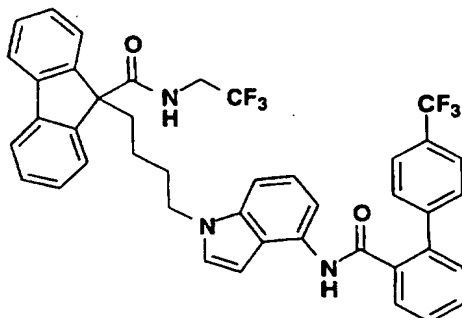
Anal. Calc'd for C₃₈H₂₉N₃O₃F₆ + 0.5 H₂O + HCl

C, 61.34; H, 4.33; N, 5.65; Cl, 4.76

Found: C, 60.90; H, 4.30; N, 5.36; Cl, 4.97.

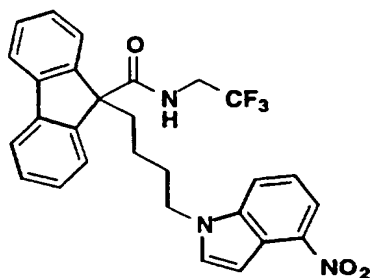
Example 418

N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-indol-1-yl]butyl]-9H-fluorene-9-carboxamide.



5

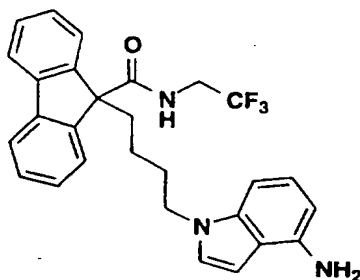
A.



A solution of 4-nitroindole (4.0 g, 24.7 mmol) in DMF (20 mL) was added slowly over 5 min to a suspension of unwashed sodium hydride (1.09 g, 60 wt.% in mineral oil, 27.2 mmol) in DMF (50 mL) at 0°C. An immediate color change to deep red occurred with bubbling of escaping gasses. The reaction mixture was stirred at 0°C for 5 min and then at RT for 40 min. A solution of Example 273 Part A(2) compound (12.6 g, 29.6 mmol) in DMF (20 mL) was added and the reaction mixture was stirred at RT over a weekend (64 h total). The solvent was removed under high vacuum on a rotary evaporator, and the resulting orange residue was partitioned between EtOAc (200 mL) and H₂O (50 mL). The organic layer was washed with H₂O (2 x 50 mL) and brine (50 mL), dried over MgSO₄, and concentrated to give a yellow foam. The crude product was purified by flash chromatography on silica gel (600 g) eluting with a step gradient of 20% to 25% to

30% EtOAc/hexane to give title compound (10.9 g, 73%) as a yellow foam.

B.

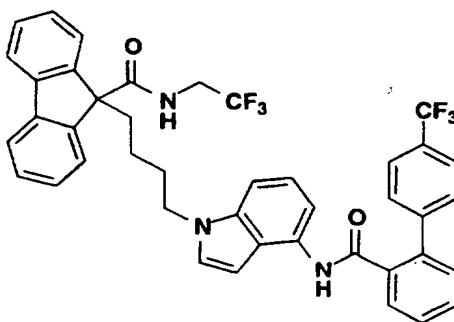


5

A mixture of Part A compound (7.47 g, 14.7 mmol) and 10% palladium on carbon (780 mg, 0.737 mmol) in EtOAc (50 mL) was hydrogenated under a balloon of H₂ at RT for 5 h, filtered through Celite[®], and washed with EtOAc (2 x 50 mL). The filtrate was concentrated and dried under high vacuum to give title compound (7.12 g, 100%) as a white foam.

15

C.



To a solution of Part B compound (5.2 g, 10.9 mmol) and triethylamine (2.0 mL, 14.2 mmol) in CH₂Cl₂ (30 mL) at 0°C was added Example 415 Part A compound (12 mL, 1.0M in CH₂Cl₂, 12.0 mmol) over 5 min. The cloudy reaction mixture was stirred at 0°C for 10 min, diluted with EtOAc (200 mL), washed with saturated NaHCO₃ (2 x 50 mL) and brine (50 mL), dried over MgSO₄, and concentrated to give a

golden foam. The crude product was dissolved in a minimal amount of CH_2Cl_2 and then purified by flash chromatography on silica gel (400 g) eluting with a step gradient of 30% to 40% EtOAc/hexane to give 5 title compound (7.74 g, 89%) as a pale yellow foam. NMR shows product to contain EtOAc.

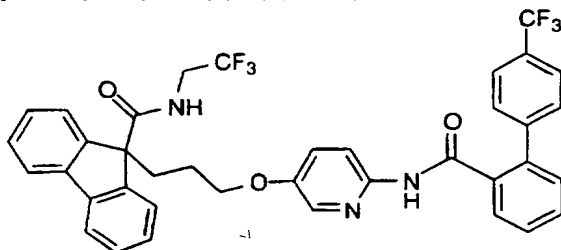
Anal. Calcd for $\text{C}_{42}\text{H}_{33}\text{F}_6\text{N}_3\text{O}_2 + 0.5 \text{ C}_4\text{H}_8\text{O}_2$:

C, 68.65; H, 4.84; N, 5.46; F, 14.81

10 Found: C, 68.38; H, 4.55; N, 5.44; F, 14.82.

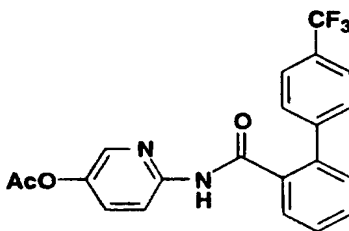
Example 419

N-(2,2,2-Trifluoroethyl)-9-[3-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-5-pyridinyl]oxy]propyl]-9H-fluorene-9-carboxamide



15

A.

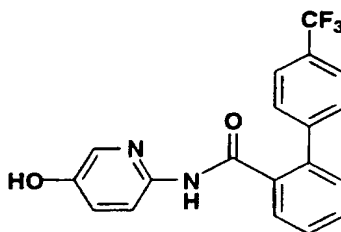


Sodium nitrite (587 mg, 8.5 mmol) was added 20 in portions to a stirred solution of 2.02 g (5.66 mmol) of Example 415 Part D compound in 40 mL of glacial AcOH at room temperature under N_2 . The reaction was stirred at room temperature for 45 minutes, then 408 mg (6.8 mmol) of urea was added 25 to destroy excess HONO and stirring was continued for 2 hours. The reaction was gradually heated to 90°C (N_2 evolution) and then 115°C , over the course of 3 hours, and then cooled to room

temperature. The solvent was removed in vacuo and the residue was taken up in CH_2Cl_2 and dilute NaHCO_3 . The CH_2Cl_2 was washed with dilute NaHCO_3 (2x) and water (2x), dried (Na_2SO_4), and concentrated to an oily residue (2.29 g). Flash chromatography over 200 g of silica gel packed in CHCl_3 by eluting with title compound (fraction A, 265 mg and fraction B, 763 mg), which was used without further purification.

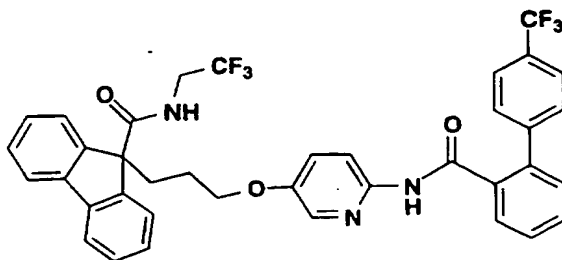
10

B.



A solution of Part A compound (763 mg) in 10 mL of CH_3OH and 6 mL of 2N KOH was stirred at room temperature for 20 hours and concentrated to a residue, which was taken up in Et_2O and water and extracted twice with Et_2O . The aqueous phase was layered with Et_2O and adjusted to pH 5.2 with dilute HCl . After two extractions with Et_2O , the acidic Et_2O extract was dried (Na_2SO_4) and concentrated to a residue. Crystallization of this residue from CH_2Cl_2 gave 439 mg of title compound. Similar treatment of the above 265 mg fraction of Part A compound provided an additional 87 mg of title compound for a total of 526 mg (26%, 2 steps) of title compound.

C.



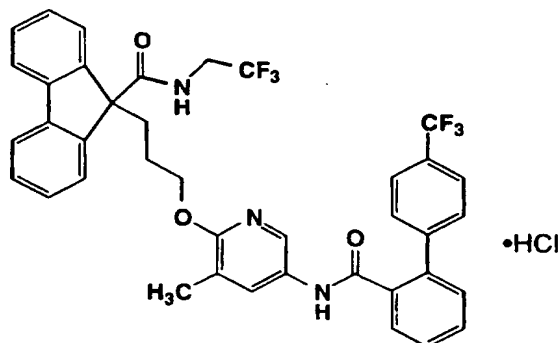
50 mg (0.143 mmol) of Example 417 Part B
5 compound, 64 mg (0.179 mmol) of Part B compound and
41 mg of triphenylphosphine were azeotropically
evaporated with toluene (3X), then dried in vacuo
for 2 hours before dissolved in 0.5 mL of freshly
distilled THF. To above solution cooled at 0°C was
10 added dropwise diethylazodicarboxylate (24.8 μ L,
0.157 mmol), and the resulting mixture was stirred
at room temperature under argon for 18 hours, then
diluted with EtOAc, washed with water, brine, dried
over MgSO_4 . The filtrate was concentrated, absorbed
15 on Celite, flash chromatographed eluting with 20-
30% EtOAc/hexane to give 76.4 mg of the product as
an oily residue. Further purification using
preparative HPLC, after lyophilization afforded
56.5 mg (57% yield) of the pure title product as a
20 white powder.

MICROANALYSIS: Calculated for $\text{C}_{38}\text{H}_{29}\text{N}_3\text{F}_6\text{O}_3 + 0.60$
 H_2O :

C, 65.16; H, 4.35; N, 6.00; F, 16.27
25 Found: C, 64.86; H, 4.04; N, 5.77; F, 16.59.
MS: (electrospray, + ions) m/e @ 690 (M+H).

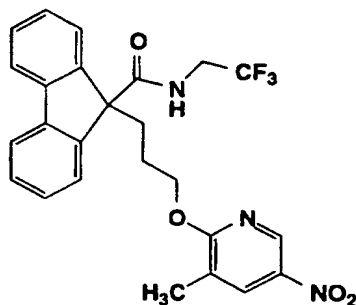
Example 420

9-[3-[[3-Methyl-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.



5

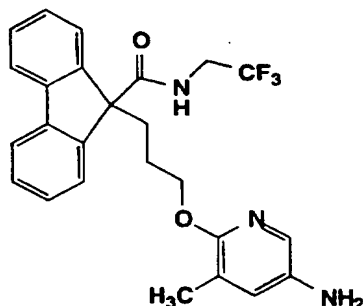
A.



A solution of Example 417 Part B compound (1.25 g, 3.58 mmol) in THF (5 mL) was treated with NaH (173 mg, 60% mineral oil dispersion, 4.3 mmol) and stirred for 15 min at RT. After all the gray solid was consumed, 2-chloro-3-methyl-5-nitropyridine (742 mg, 4.3 mmol) was added to the reaction mixture. The resulting black mixture was stirred at RT for 18 h. Additional 2-chloro-3-methyl-5-nitropyridine (74 mg, 0.43 mmol) was added and stirring was continued for 6 h longer. The mixture was diluted with 5% aq. NaHCO₃ (10 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with H₂O (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated to give a foam. Flash chromatography on Merck silica gel K-60 (50 g) eluting with EtOAc/hexane

(0.5:9.5 to 1:4) to give title compound (1.53 g, 90%) as a solid, m.p. 102-104°C.

B.

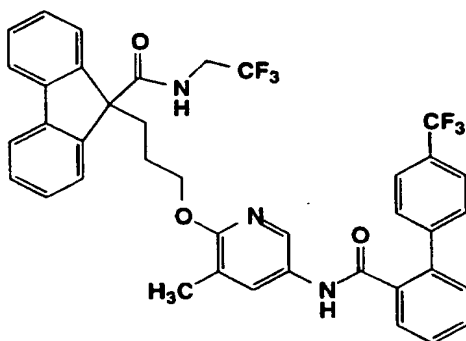


5

A mixture of Part A compound (250 mg, 0.51 mmol) and 10% palladium on carbon (15 mg) in ethyl acetate (5 mL) was hydrogenated (balloon pressure) at RT for 24 h. The catalyst was removed by filtration through nylon 66 filter, and concentrated in vacuo to give crude title amine (240 mg, quantitative) as an oil.

15

C.



To a solution of crude Part B compound (240 mg, 0.50 mmol) and triethylamine (221 μ l, 1.5 mmol) in CH_2Cl_2 (5 mL) at 0°C was added dropwise 540 μ l (0.54 mmol) of 1.0 M 4'-(trifluoromethyl)-2-biphenyl carboxylic acid chloride (Example 415 Part A) solution in CH_2Cl_2 . The reaction was stirred at 0°C for 1 h. Dichloromethane (20 mL) was added and the solution was washed with sat. NaHCO_3 solution

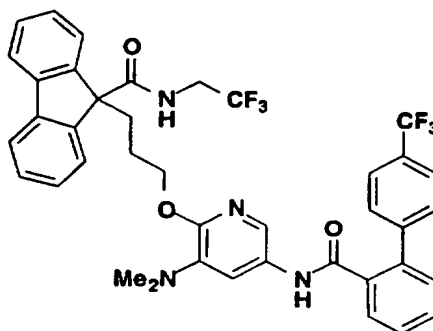
(2 x 10 mL), then dried over Na₂SO₄ and concentrated to give an oil. Purification by flash chromatography on Merck silica gel K-60 (20 g) eluting with CH₂Cl₂/MeOH (10:0 to 9.8:0.2) to give
5 300 mg of title compound as a free base. To the stirred solution of free base title compound (281 mg, 0.4 mmol) in THF was added 4N HCl in dioxane (415 µl, 1.6 mmol). After stirring for 3 min, the clear solution was diluted with Et₂O (50 mL). The
10 separated solid was collected and dried in vacuo (0.5 mm) at RT for 2 h to give title compound (260 mg, 90%) as off white solid.

MS (ESI, + ions) m/z 704 (M + H).

15

Example 421

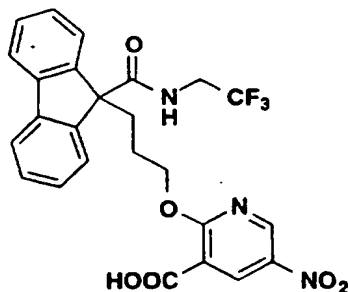
9-[3-[[3-(Dimethylamino)-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



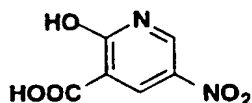
20

For compounds of Part A(1) and Part A(2), the procedure described in J. Med. Chem. **1992** 35, 1895, was followed.

A.



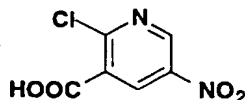
A(1).



5

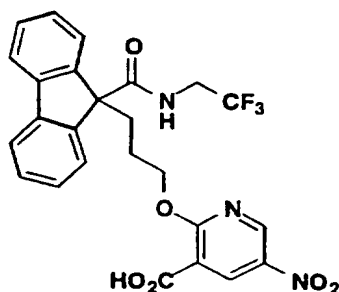
Fuming nitric acid (10 mL, 240 mmol) was added to a suspension of 2-hydroxynicotinic acid (13.9 g, 100 mmol) in concentrated sulfuric acid (40 mL) and the reaction mixture was heated gradually to 50°C, at which point all solids had dissolved. After 5 min at 50°C, the reaction mixture began to exotherm violently, whereupon the heating bath was removed. The reaction mixture turned dark red and emitted red fumes, and within a few minutes, began to cool down. Once at RT (HPLC indicated complete reaction), the yellow solution was poured into ice water (600 mL), and the resulting solid was filtered, washed with ice water (2 x 100 mL), and air-dried for 1 h to give 12.1 g of a yellow solid. The crude product was recrystallized from H₂O (200 mL) and then dried in a vacuum oven at 90 °C to give title compound (10.4 g, 57%) as a yellow solid (mp 238.5-240.5°C, lit mp 240°C).

A(2).



A suspension of Part A(1) compound (7.0 g, 38 mmol) in phosphorus oxychloride (20 mL) was heated at reflux for 2 h, cooled to RT, and added slowly to H₂O (100 mL) with stirring, maintaining the temperature below 40°C with added ice. Following addition, the mixture was stirred at RT for 30 min, whereupon a precipitate formed. The mixture was extracted with Et₂O/THF (2:1, 2 x 200 mL), and the combined organic extracts were washed with brine (100 mL), dried over Na₂SO₄, and concentrated to give an oily yellow solid. The crude product was taken up in hot Et₂O/hexane (1:1, 200 mL), filtered, and the filtrate was concentrated to give title compound (5.78 g, 75%) as a yellow solid (mp 140-141°C, lit mp 142-143°C).

20 A(3).

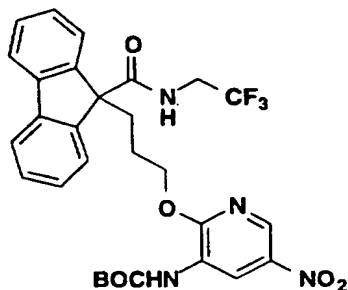


Sodium hydride (124 mg, 60 wt% in mineral oil, 3.09 mmol) was added all at once to a solution of Example 417 Part B compound (430 mg, 1.23 mmol) in DMF (2 mL). After evolution of gasses, the reaction mixture was stirred for 30 min at RT, followed by addition of Part A(2) compound (208 mg, 1.03 mmol) all at once. Bubbling ensued and the reaction mixture was stirred at RT for 30 min, diluted with H₂O, and then acidified with 1N HCl (3

mL). The solid mass that formed was extracted with EtOAc (20 mL), washed with a large amount of brine, dried over Na_2SO_4 , and concentrated to give 750 mg crude title carboxylic acid as a yellow oil.

5

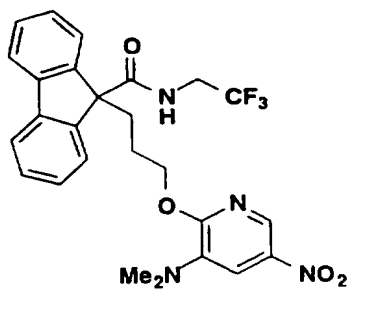
B.



Diphenylphosphoryl azide (477 μL , 2.22 mmol) was added to a solution of Part A compound (955 mg, 1.85 mmol) and triethylamine (385 μL , 2.78 mmol) in freshly distilled *tert*-butanol. The reaction mixture was heated at 80°C for 2 h, cooled to RT, and concentrated to give an orange oil. The oil was dissolved in EtOAc (25 mL), washed with saturated NaHCO_3 (2 x 5 mL), H_2O (5 mL), and brine (5 mL), dried over MgSO_4 , and concentrated to give 1.33 g of an orange thick oil. The crude product was purified by flash chromatography on silica gel (100 g) eluting with a step gradient of 15% to 20% EtOAc/hexane to give title compound (355 mg, 33%) as a yellow foam.

20

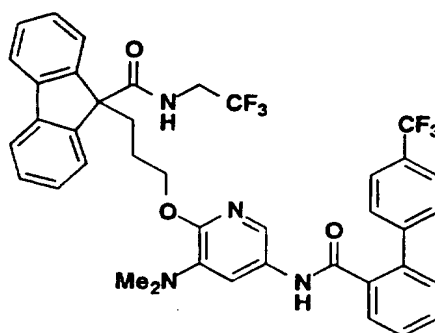
C.



25

A solution of Part B compound (343 mg, 0.585 mmol) in 4N HCl/dioxane (3 mL) was allowed to stand at RT for 5 h, then concentrated to give the crude amine. To a mixture of the crude free amine, formalin (950 μ L, 37%, 11.7 mmol), and AcOH (1 mL, 17.6 mmol) in MeOH (3 mL) was added sodium cyanoborohydride (370 mg, 5.85 mmol) all at once. The reaction mixture was stirred at RT overnight, concentrated, and azeotroped with toluene (15 mL). The residue was dissolved in EtOAc (50 mL), washed with saturated NaHCO₃ (2 x 10 mL) and brine (10 mL), dried over MgSO₄, and concentrated to give 400 mg of an orange oil. The crude product was purified by flash chromatography on silica gel (50 g) eluting with 15% EtOAc/hexane to give title compound (230 mg, 76%) as a yellow glass.

D.



20

Following the procedure in Example 418 Part C compound (230 mg, 0.447 mmol) was hydrogenated and then acylated with Example 415 Part A compound to give title compound (234 mg, 72%) as a white foam.

25

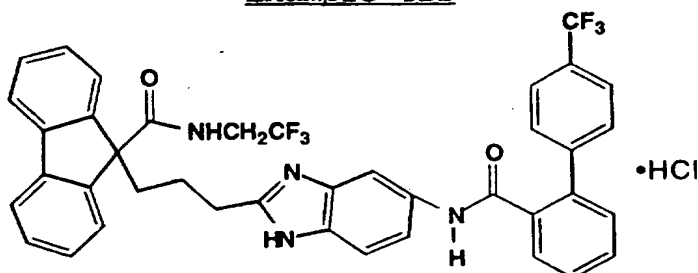
MS (ES, + ions) m/z 733 [M+H].

Anal. Calcd for C₄₀H₃₄F₆N₄O₃ + 0.5 H₂O:

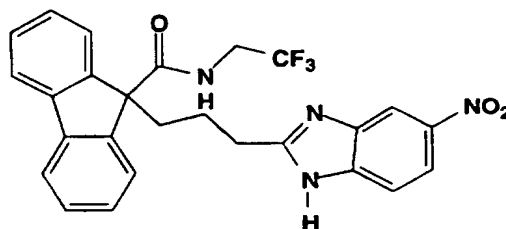
C, 64.77; H, 4.76; N, 7.55; F, 15.37

Found: C, 64.70; H, 4.60; N, 7.28; F, 15.16.

30

Example 422

A.

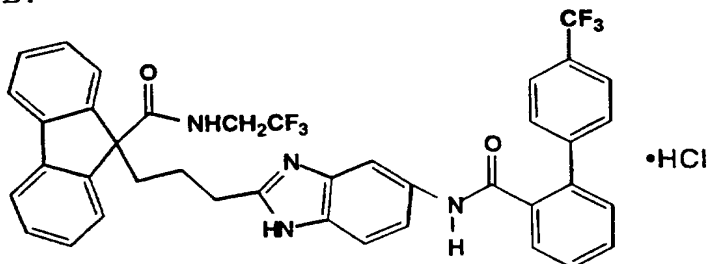


5

A mixture of Example 416 Part B compound (400 mg, 1.11 mmoles), 5-nitrophenyldiamine (173 mg, 1.11 mmoles) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (256.3 mg, 1.11 mmoles) in dry CH_3CN (5.0 ml) was stirred at room temperature for 25 hours and stripped to dryness. The crude mixture chromatographed on a silica gel column (Merck), eluting the column with $\text{CH}_2\text{Cl}_2\text{:EtOAc}$ (3:1) to give title compound as a light brick-red solid foam (313 mg, 57.1 %).

TLC : R_f 0.47 (Silica gel; $\text{EtOAc:CH}_2\text{Cl}_2$ -6:4; UV)

B.



20

A solution of Part A compound (308 mg, 0.62 mmole) in dry CH_3OH (15 ml) was treated with 10%

Pd/C (60 mg) and hydrogenated (balloon) at room temperature for 19 hours. The reaction mixture was diluted with CH₃OH (15 ml) and filtered through a celite pad in a millipore unit, washing the pad well with CH₃OH (3x). The combined filtrates were evaporated to dryness and dried in vacuo to give the crude amine as a syrup (281.7 mg).

The amine was dissolved in dry CH₂Cl₂ (8.0 ml), treated with 4'-(trifluoromethyl)-2-biphenyl-carboxylic acid (167 mg, 0.65 mmole), HOBt·H₂O (86 mg, 0.64 mmole) and EDAC (133.4 mg, 0.68 mmole) and stirred at room temperature for 20 hours. The reaction mixture was partitioned between EtOAc (2 x 25 ml) and saturated NaHCO₃ (4.5 ml) and the combined organic extracts were washed with H₂O (3x) and brine, dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried in vacuo. The crude product mixture was chromatographed on a silica gel column (Merck), eluting the column with EtOAc:Hexane mixtures (1:2; 4:1) to give the clean free base (165.7 mg, 37.3%).

This adduct (136 mg, 0.19 mmole) was dissolved in dry dioxane (1.7 ml), treated with 4.0 M HCl/dioxane (0.17 ml, 3.5 eq), swirled for a few minutes then diluted with dry Et₂O (25 ml), scratching the solids as they formed. The mixture was filtered and the solids washed with dry Et₂O (2x) to give title compound as a solid (123 mg, m.p. 170-180°C, shrinking commencing at 150°C).

30

MS: (M + H)⁺ = 713.

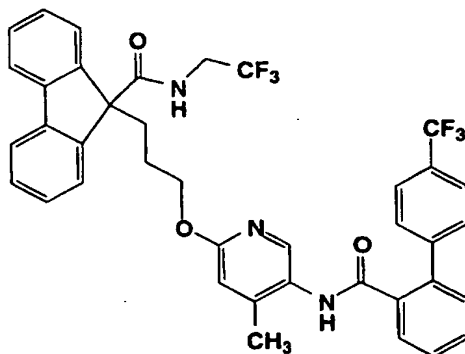
Anal. Calc'd for C₄₀H₃₀F₆N₄O₂·HCl·0.9 H₂O:

C, 62.77; H, 4.32; N, 7.32; Cl, 4.63; F, 14.89

35 Found: C, 62.73; H, 4.00; N, 7.22; Cl, 4.60; F, 14.51

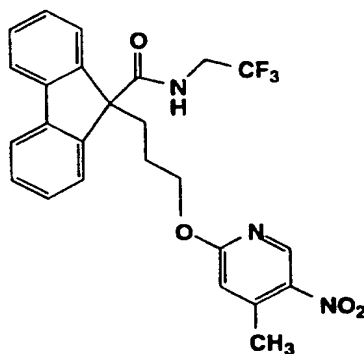
Example 423

9-[3-[[4-Methyl-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



5

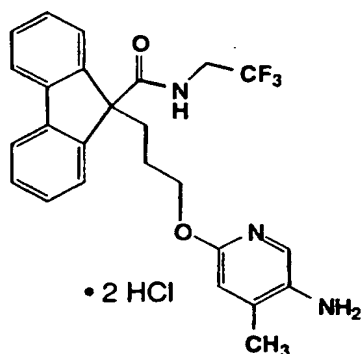
A.



To a stirred solution of Example 417 Part B compound (7.0 g, 20.0 mmol, dried with toluene) in
 10 200 mL of dry THF at 0°C under argon was added triphenylphosphine (7.9 g, 30.0 mmol) and 2-hydroxy-4-methyl-5-nitropyridine (3.7 g, 24.0 mmol) followed by the dropwise addition of diisopropyl azodicarboxylate (DIAD) (5.9 mL, 30.0 mmol). The
 15 reaction mixture was stirred at 0°C for 1 h and quenched with sat. NaHCO₃ (70 mL) and concentrated to remove THF. Water (300 mL) was added and the mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with H₂O (100
 20 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated in vacuo to give a viscous oil. Flash chromatography on Merck silica gel K-60 (800 g)

eluting with EtOAc/hexane (0.5:9.5 to 1:4) provided 4.0 g (41%) of title compound as foam.

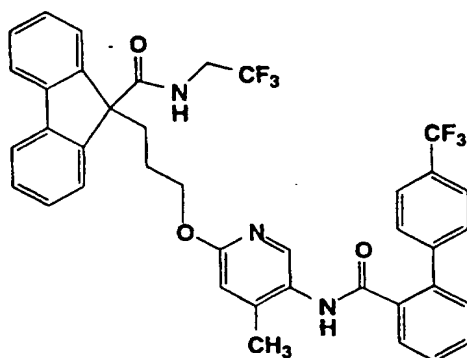
B.



5

A mixture of Part A compound (1.5 g, 3.09 mmol) and 10% palladium on carbon (200 mg) in ethyl acetate (30 mL) was hydrogenated (balloon pressure) at RT for 24 h. TLC showed the presence of some starting material; therefore an additional quantity of 10% Pd/C (25 mg) was added and hydrogenation was continued for 12 h longer. The catalyst was removed by filtration through nylon 66 filter, and concentrated in vacuo to give crude amine. To the stirred solution of clear amine in Et₂O (100 mL) was added 4N HCl in dioxane (2.8 mL, 10.7 mmol). The separated solid was diluted with Et₂O (50 mL) and collected, dried in vacuo (0.5 mm) at RT for 3 h to give title compound (1.53 g, 94%) as off white solid.

C.



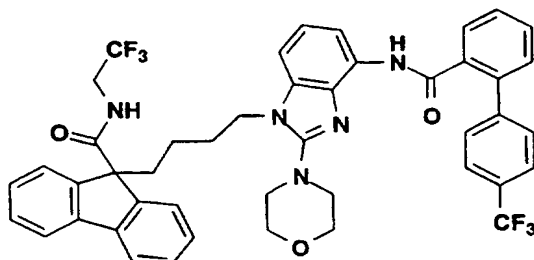
- To a solution of crude Part B compound (106 mg, 0.2 mmol) and triethylamine (150 μ l, 1.0 mmol) in CH_2Cl_2 (5 mL) at 0°C was added dropwise 220 μ l of 1.0 M 4'-(trifluoromethyl)-2-biphenyl acid chloride solution in CH_2Cl_2 (0.22 mmol). The reaction was stirred at 0°C for 1 h.
- Dichloromethane (20 mL) was added and the solution was washed with sat. NaHCO_3 solution (2 x 5 mL), then dried over Na_2SO_4 and concentrated to give 190 mg of foam. Purification by flash chromatography on Merck silica gel K-60 (5 g) eluting with EtOAc/hexane (1:4 to 3:7) provided title compound (110 mg, 78%) as foam.

MS (ESI, + ions) m/z 704 ($M + H$).

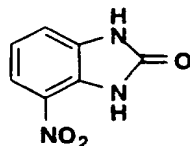
20

Example 424

9-[4-[2-(4-Morpholinyl)-4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



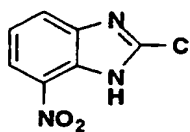
A.



To a solution of 3-nitro-1,2-benzenediamine
5 (5.36 g, 35 mmol) in 300 mL of dry THF cooled at
0°C was added Et₃N (10.95 mL), followed by dropwise
addition of phosgene/toluene (1.93 M, 20 mL, 38.5
mmol). After addition, the resulting suspension
was stirred at room temperature overnight, then
10 filtered. The collected solid was washed with H₂O
(4X), dried over P₂O₅ in vacuo for 2 days to give
3.98 g (63% yield) of title compound as a brown
solid.

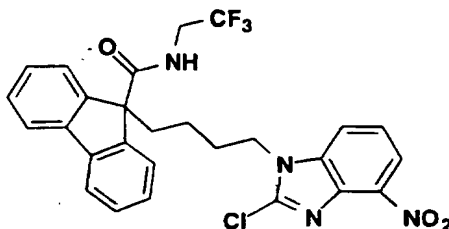
15

B.



A suspension of Part A compound (3.583 g,
20 mmol) in 70 mL of POCl₃ was refluxed at 120°C
20 for 3 hours, then a stream of HCl gas was bubbled
through a gently refluxed suspension for 2 more
hours. After cooling to room temperature, the
reaction mixture was concentrated in vacuo to
dryness. The obtained residue was dissolved in
25 H₂O, adjusted pH to 6 with 10% aqueous NH₄OH, then
extracted with EtOAc (3X). The combined EtOAc
extracts were washed with H₂O (2X), brine, dried
over MgSO₄. The filtrate was concentrated and the
residue was absorbed on Celite, then
30 chromatographed eluting with 25% EtOAc/hexane to
give 2.785 g (71% yield) of title compound as a
light yellow solid.

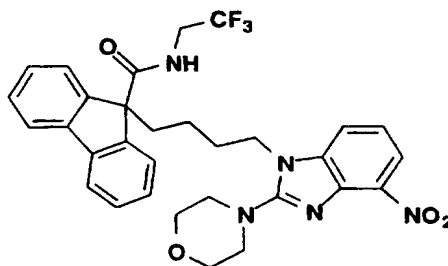
C.



To a solution of Part B compound (2.785 g, 14.10 mmol) in 30 mL of anhydrous DMF was added 7.20 g (16.92 mmol) of Example 273 Part A(2) compound, followed by potassium carbonate (3.90g, 28.20 mmol). The resulting suspension was stirred at room temperature under argon for 64 hours, then partitioned between EtOAc/H₂O. The aqueous phase was extracted with EtOAc (3X), the combined EtOAc extracts washed with water (3X), brine, dried over MgSO₄. The filtrate was concentrated in vacuo to give a beige colored solid, which was triturated with EtOAc (2X), dried in air to yield 2.3 g of title compound as an off-white solid. The EtOAc washings were concentrated and the residue triturated with EtOAc, and the process repeated to afford 1.9 g more of title compound. The EtOAc washings from last trituration were concentrated and the residue absorbed on Celite, then chromatographed eluting with 20-50% EtOAc/hexane to give additional 0.4 g of title compound (total 4.6 g, 60% yield) as a light yellow solid.

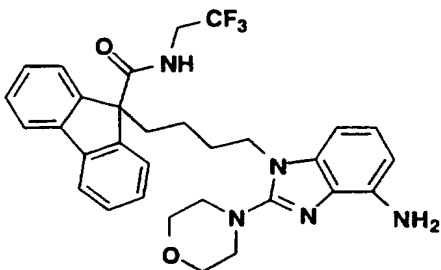
25

D.



A solution of Part C compound (109 mg, 0.20 mmol) in neat morpholine (1 mL) was heated at 45°C under argon for 20 hours, then concentrated to dryness, the residue chromatographed eluting with
5 50-70% EtOAc/hexane to give 123 mg (100% yield) of title compound as a yellow foam.

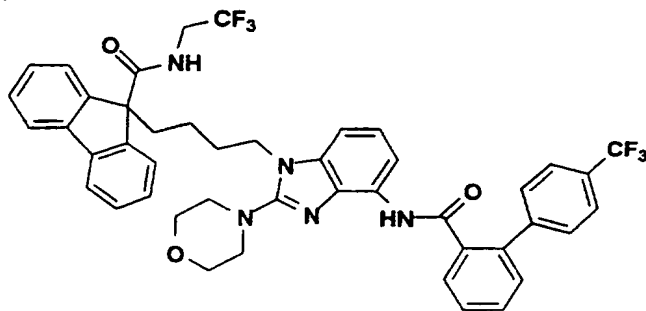
E.



10

A suspension of Part D compound (115 mg, 0.2 mmol) and 45 mg of 10% Pd/C in EtOH/EtOAc (1:1, 4 mL) was hydrogenated under a hydrogen balloon for 3.5 hours, then filtered. The filtrate
15 was concentrated, the residue stripped with CH₂Cl₂ (3X), dried in vacuo to give 110 mg (100% yield) of title compound as a white foam.

F.



20

To a solution of Part E compound (110 mg, 0.2 mmol) in 0.5 mL of CH₂Cl₂ cooled at 0°C was added a 1.0 M solution of Example 415 Part A
25 compound in CH₂Cl₂ (0.24 mL), followed by Et₃N (35 μL). The resulting mixture was stirred at room temperature under argon overnight, then diluted

with EtOAc, washed with water, brine, dried over
MgSO₄. The filtrate was concentrated in vacuo, the
obtained residue absorbed on Celite,
chromatographed eluting with 20-60% EtOAc/hexane to
5 give 110 mg of title compound as a white foam,
which was lyophilized in MeOH/H₂O to give 100 mg
(61% yield) of title compound as a white powder.

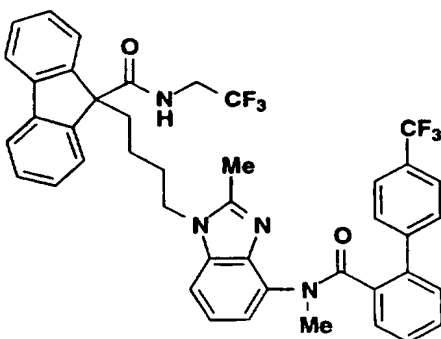
MS: (electrospray, + ions) m/e @ 812 (M+H).

10 MS: (high resolution) Calcd for C₄₅H₄₀N₅F₆O₃ (M+H),
812.3055

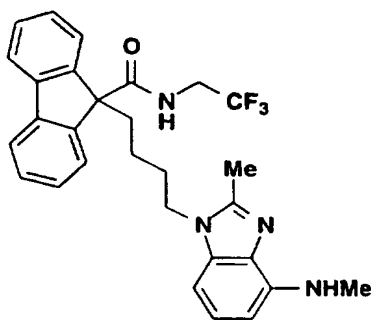
Found: 812.2994.

Example 425

15 9-[4-[2-Methyl-4-[methyl[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-
1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



A



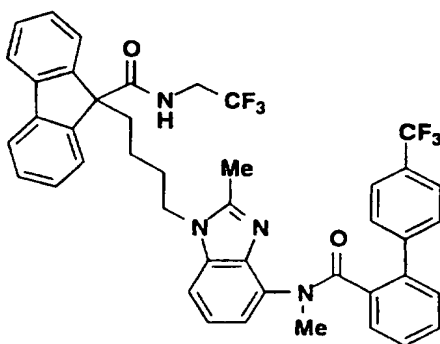
20

Acetic anhydride (472 μ L, 5 mmol) was added
to formic acid (5.0 mL) at 0°C. The reaction
mixture was stirred at 0°C for 30 min, and a
portion (1.9 mL, 1.9 mmol) was added slowly to a

solution of Example 410 Part C compound (300 mg, 0.61 mmol) in THF (0.5 mL) at 0°C. After 30 min, the reaction mixture was partitioned between EtOAc (20 mL) and saturated NaHCO₃ (20 mL), and the organic layer was washed with saturated NaHCO₃ (5 mL) and brine (5 mL), dried over Na₂SO₄, and concentrated to give 189 mg of the formamide.

Lithium aluminum hydride (515 µL, 1.0M in THF, 0.515 mmol) was added dropwise to a solution of a portion of the formamide (312 mg) in THF (3 mL) at 0°C. The cooling bath was removed, and the reaction mixture was stirred at RT for 30 min. Following a quench with H₂O (0.5 mL), 1M sodium potassium tartrate (5 mL) was added, and the reaction mixture was stirred at RT vigorously for 2 h. The reaction mixture was extracted with EtOAc (2 x 10 mL), and the organic extracts were washed with brine (5 mL), dried over Na₂SO₄, and concentrated to give 110 mg of an opaque oil. The crude product was purified by flash chromatography on silica gel (35 g) eluting with a step gradient of 60% to 80% EtOAc/hexane to give title compound (280 mg, 89%) as a yellow foam.

25 B.



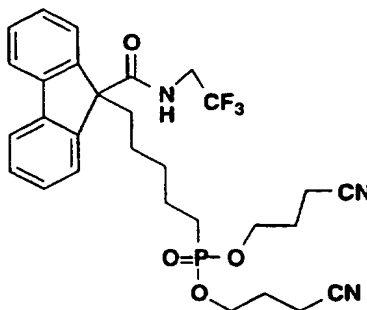
Following the procedure in Example 418 Part C, Part A compound (218 mg, 0.431 mmol) was acylated with Example 415 Part A compound to give title compound (289 mg, 89%) as a white foam.

MS (ES, + ions) m/z 741 [M+H].

The following additional compounds were
5 prepared employing procedures described
hereinbefore.

Example 426

9-[5-[Bis(3-cyanopropoxy)phosphinyl]pentyl]-N-(2,2,2-trifluoroethyl)-
9H-fluorene-9-carboxamide.

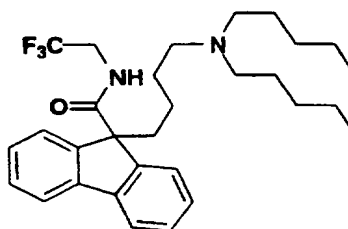


10

MS (ESI, + ions): 576 (M+H), 593 (M+NH₄).

Example 427

9-[4-(Dipentylamino)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-
9-carboxamide, monohydrochloride.

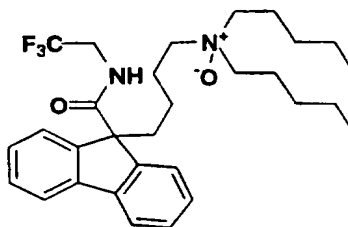


15

MS (electrospray, - ions) m/z 503 (M+H).

Example 428

9-[4-(Dipentylamino)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-
9-carboxamide, N-oxide.

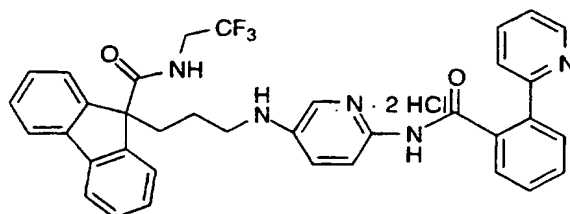


20

MS (electrospray, - ions) m/z 519 (M+H).

Example 429

9-[3-[[2-[(2-Pyridinyl)benzoyl]amino]-5-pyridinyl]amino]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

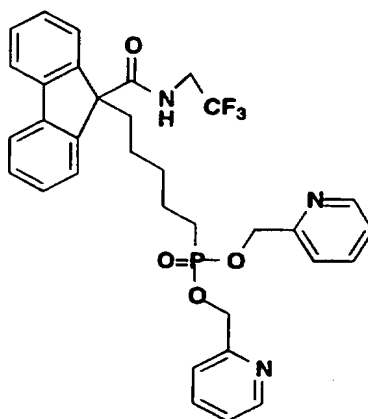


MS (ESI-NH₃, + ion) 622 [M+H]; (-ion) 620 [M-H].

5

Example 430

[5-[9-[[2,2,2-Trifluoroethyl]amino]carbonyl]-9H-fluoren-9-yl]pentyl]phosphonic acid, bis(2-pyridinylmethyl) ester.

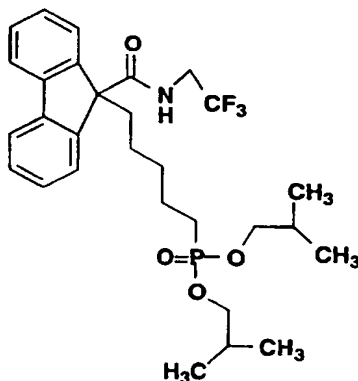


MS (ESI, + ions): 624 (M+H).

10

Example 431

[5-[9-[[2,2,2-Trifluoroethyl]amino]carbonyl]-9H-fluoren-9-yl]pentyl]phosphonic acid, bis(2-methylpropyl) ester.

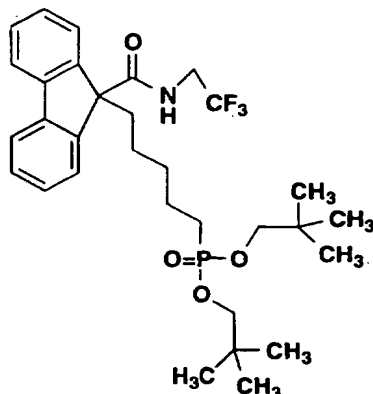


MS (ESI, + ions): 554 (M+H), 571 (M+NH₄).

15

Example 432

[5-[9-[[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluorene-9-yl]pentyl]phosphonic acid, bis(2,2-dimethylpropyl) ester.

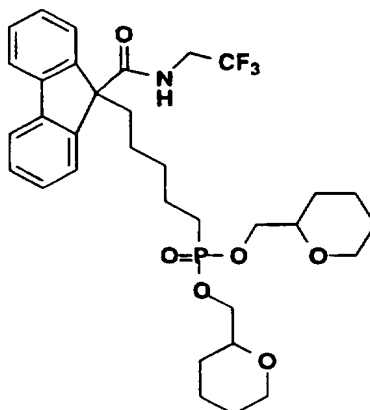


MS (ESI, + ions): 582 (M+H), 599 (M+NH₄).

5

Example 433

[5-[9-[[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluorene-9-yl]pentyl]phosphonic acid, bis(tetrahydro-2H-pyran-2-ylmethyl) ester.

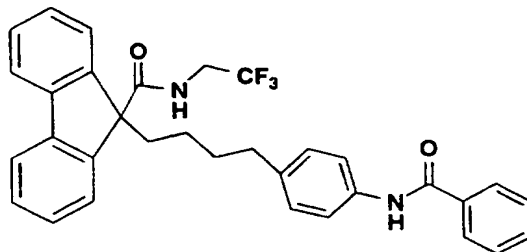


MS (ESI, + ions): 638 (M+H), 655 (M+NH₄).

10

Example 434

9-[4-[4-(Benzoylamino)phenyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

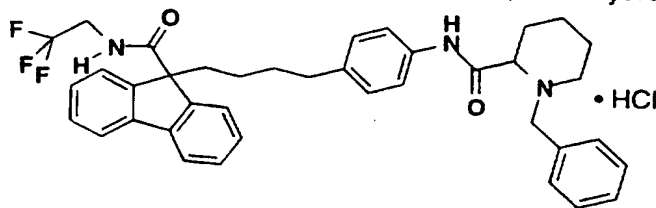


MS (electrospray, + ions) m/z 543 (M+H).

15

Example 435

9-[4-[4-[[[1-(Phenylmethyl)-2-piperidiny]carbonyl]amino]phenyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

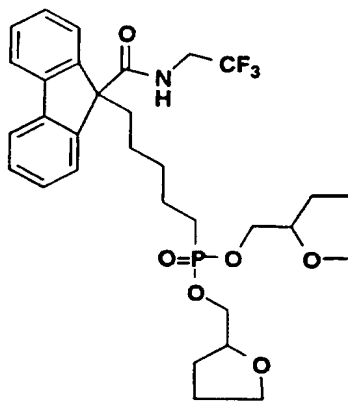


MS (electrospray, + ions) m/z 640 (M+H).

5

Example 436

[5-[9-[[[2,2,2-Trifluoroethyl]amino]carbonyl]-9H-fluorene-9-yl]pentyl]phosphonic acid, bis(tetrahydrofuran-2-ylmethyl) ester.

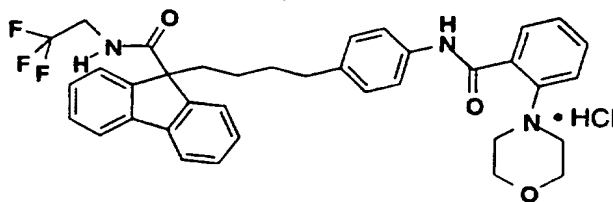


MS (ESI, + ions): 610 (M+H), 627 (M+NH₄); (-ion)

10 608 (M-H).

Example 437

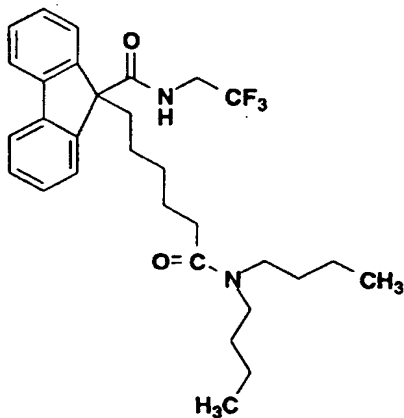
9-[4-[4-[[2-(4-Morpholinyl)benzoyl]amino]phenyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.



15 MS (electrospray, + ions) m/z 628 (M+H).

Example 438

9-[6-(Dibutylamino)-6-oxohexyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

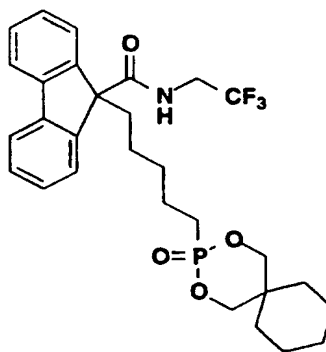


MS (ESI, + ion): 517 (M+H).

5

Example 439

9-[5-(3-Oxo-2,4-dioxo-3-phosphaspiro[5.5]undecan-3-yl)pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

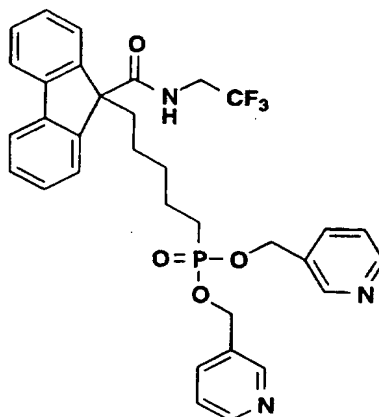


MS (ESI, + ion): 550 (M+H).

10

Example 440

[5-[9-[[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]pentyl]phosphonic acid, bis(2-pyridinylmethyl) ester.

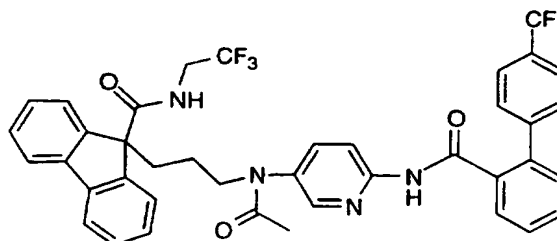


MS (ESI, - ion): 622 (M-H).

5

Example 441

9-[3-[Acetyl[2-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-5-pyridinyl]amino]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

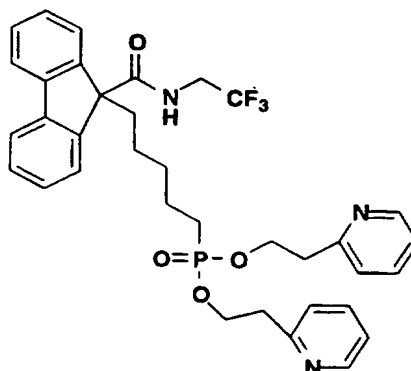


MS (M+H)⁺ @ 731.

10

Example 442

[5-[9-[[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]pentyl]phosphonic acid, bis[2-(2-pyridinyl)ethyl] ester.

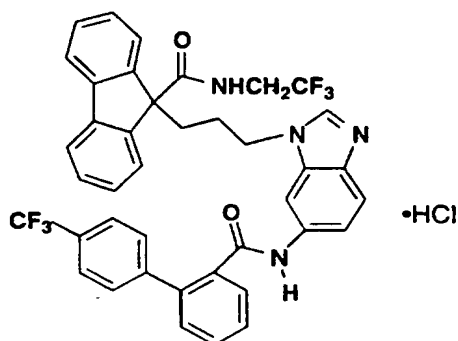


MS (ESI, + ion): 652 (M+H).

15

Example 443

N-(2,2,2-Trifluoroethyl)-9-[3-[6-[[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-9H-fluorene-9-carboxamide, monohydrochloride.

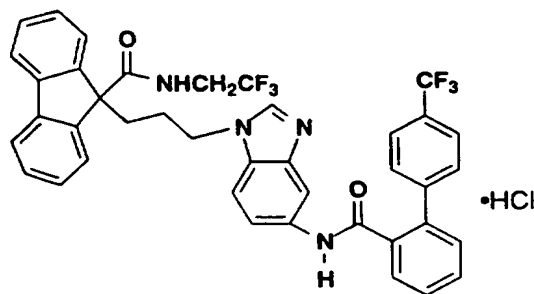


MS: $(M+H)^+ = 713$.

5

Example 444

N-(2,2,2-Trifluoroethyl)-9-[3-[5-[[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-9H-fluorene-9-carboxamide, monohydrochloride.

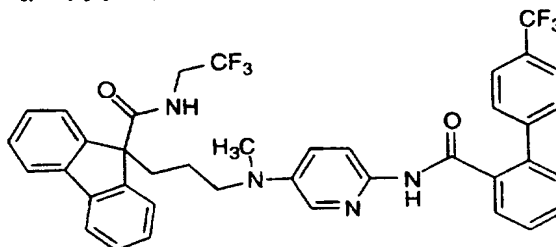


MS: $(M+H)^+ = 713$.

10

Example 445

9-[3-[Methyl[2-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-5-pyridinyl]amino]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

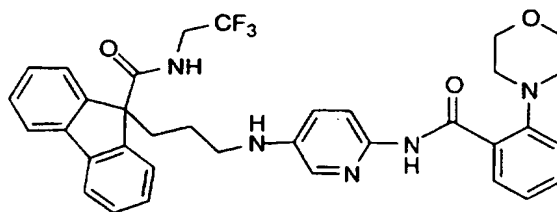


MS: $(M+H)^+ @ 703$.

15

Example 446

9-[3-[[2-[(4-Morpholinyl)benzoyl]amino]-5-pyridinyl]amino]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



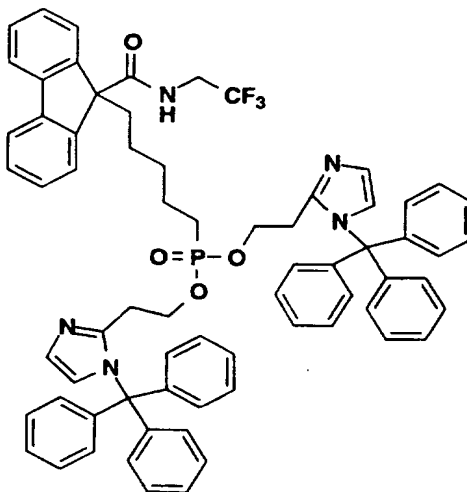
• HCl salt

MS: (M+H)⁺ @ 630.

5

Example 447

[5-[9-[[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]pentyl]phosphonic acid, bis[2-[1-(triphenylmethyl)-1H-imidazol-2-yl]ethyl] ester.

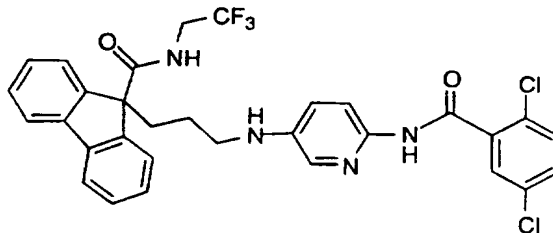


MS (ESI, + ion): 1114 (M+H).

10

Example 448

9-[3-[[2-[(2,5-Dichlorobenzoyl)amino]-5-pyridinyl]amino]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

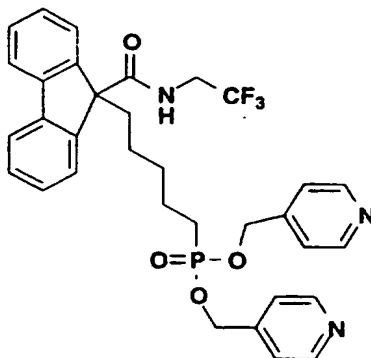


MS: (M+H)⁺ @ 613.

15

Example 449

[5-[9-[[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]pentyl]phosphonic acid, bis(4-pyridinyl)methyl ester.

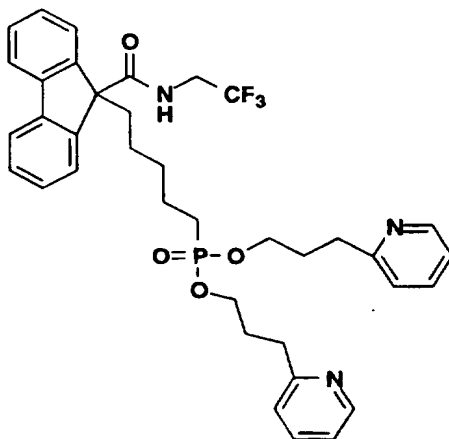


MS (ESI, + ion): 624 (M+H).

5

Example 450

[5-[9-[[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]pentyl]phosphonic acid, bis[3-(2-pyridinyl)propyl] ester.

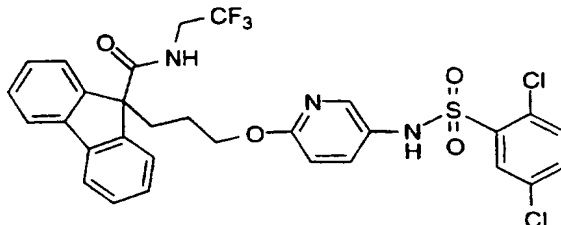


MS (ESI, + ion): 680 (M+H).

10

Example 451

9-[3-[[[5-[[[(2,5-Dichlorophenyl)sulfonyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

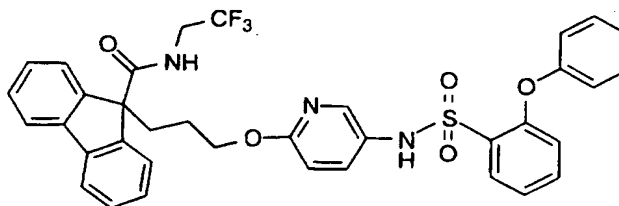


MS: (M+H)⁺ @ 650; MW 649.

15

Example 452

9-[3-[[5-[[[2-Phenoxyphenyl)sulfonyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

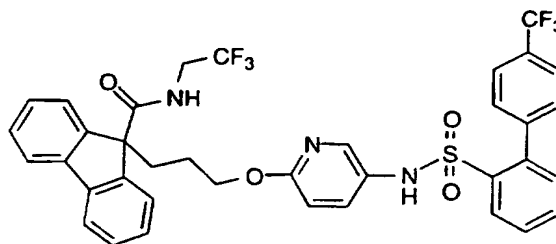


MS: (M+H) = @ 673

5

Example 453

N-(2,2,2-Trifluoroethyl)-9-[3-[[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl)sulfonyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

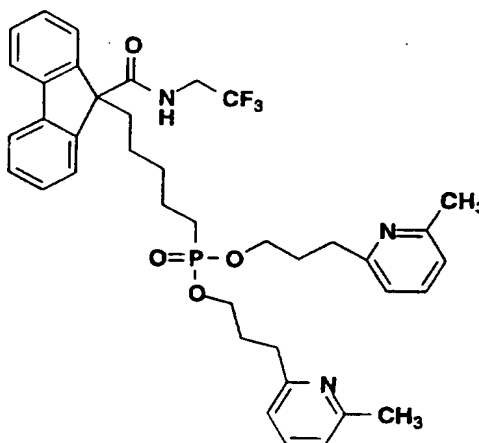


MS: (M+H) + @ 726.

10

Example 454

[5-[9-[[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]pentyl]phosphonic acid, bis[3-(6-methyl-2-pyridinyl)propyl] ester.

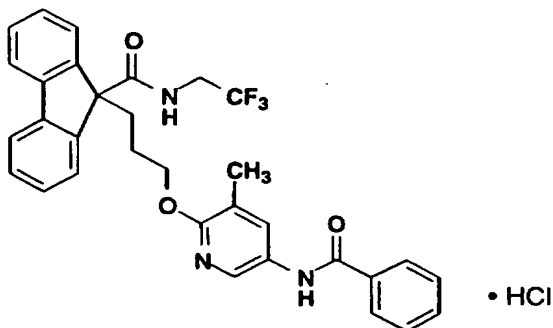


MS (ESI, - ion): 706 (M-H).

15

Example 455

9-[3-[[5-(Benzoylamino)-3-methyl-2-pyridinyl]-oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

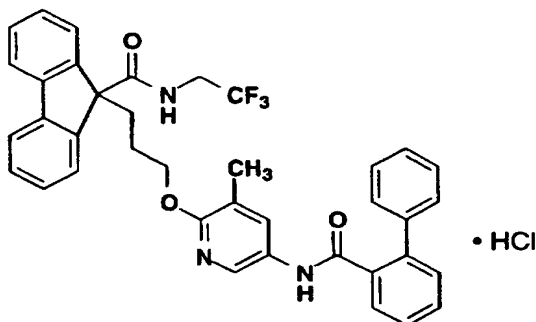


MS (ESI, + ion): 560 (M+H).

5

Example 456

9-[3-[[5-[[[1,1'-Biphenyl]-2-yl]carbonyl]amino]-3-methyl-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

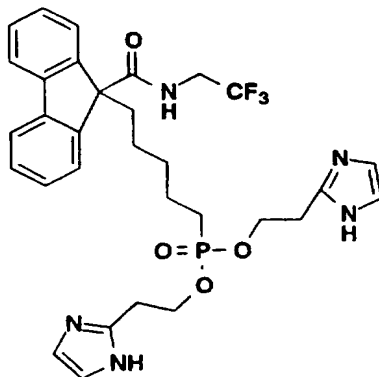


MS (ESI, + ion): 636 (M+H).

10

Example 457

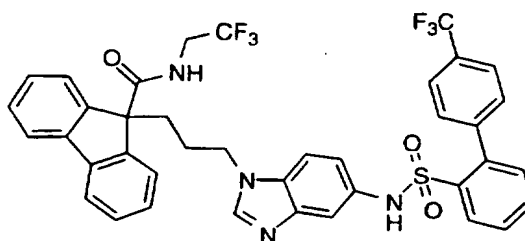
[5-[9-[[2,2,2-Trifluoroethyl]amino]carbonyl]-9H-fluoren-9-yl]pentyl]phosphonic acid, bis 2-(1H-imidazol-2-yl)ethyl ester.



MS (ESI, + ion): 630 (M+H).

Example 458

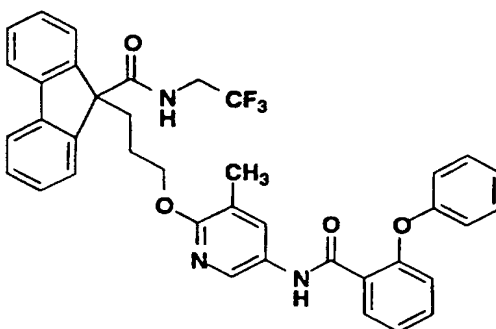
N-(2,2,2-Trifluoroethyl)-9-[3-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]sulfonyl]amino]-1H-benzimidazol-1-yl]propyl]-9H-fluorene-9-carboxamide.



5 MS: (M+H)⁺ @ 749; (M-H) @ 747.

Example 459

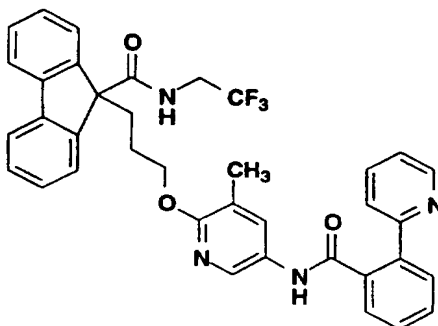
9-[3-[[3-Methyl-5-[(2-phenoxybenzoyl)amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



10 MS (ESI, + ion): 652 (M+H).

Example 460

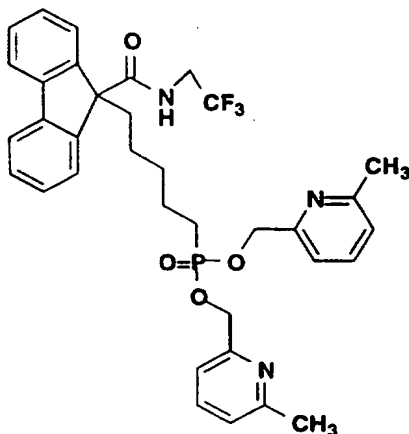
9-[3-[[3-Methyl-5-[[2-(2-pyridinyl)benzoyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



15 MS (ESI, + ion): 637 (M+H).

Example 461

[5-[9-[[2,2,2-Trifluoroethyl]amino]carbonyl]-9H-fluoren-9-yl]pentyl]phosphonic acid, bis[(6-methyl-2-pyridinyl)methyl] ester.

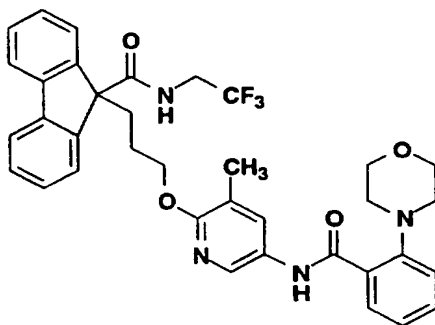


MS (ESI, + ions): 652 (M+H).

5

Example 462

9-[3-[[3-Methyl-5-[[2-(4-morpholinyl)benzoyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

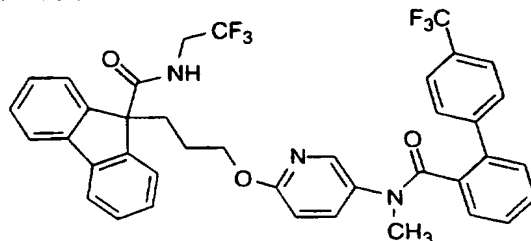


MS (ESI, + ion): 645 (M+H).

10

Example 463

9-[3-[[5-[Methyl[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]sulfonyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

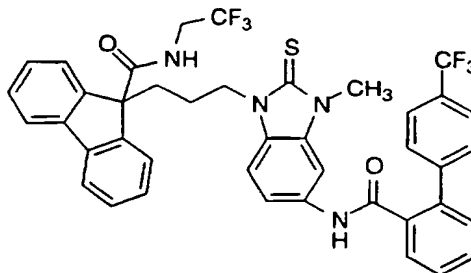


MS: (M+H)⁺ @ 704, (M-H) @ 702.

15

Example 464

9-[3-[2,3-Dihydro-3-methyl-2-thioxo-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

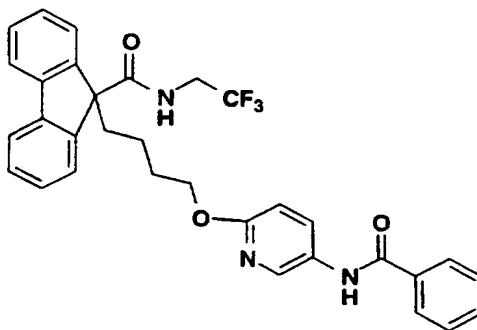


MS: (M+H)⁺ @ 759+

5

Example 465

9-[4-[[5-(Benzoylamino)-2-pyridinyl]oxy]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

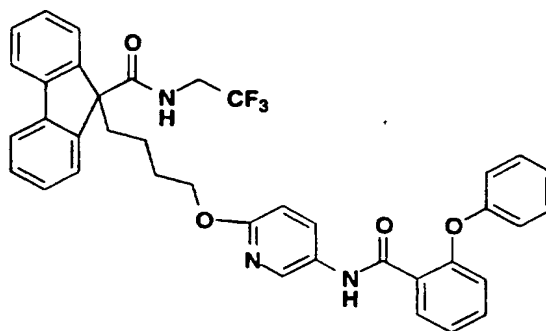


MS (ESI, + ion): 560 (M+H).

10

Example 466

9-[4-[[5-[(2-Phenoxybenzoyl)amino]-2-pyridinyl]oxy]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

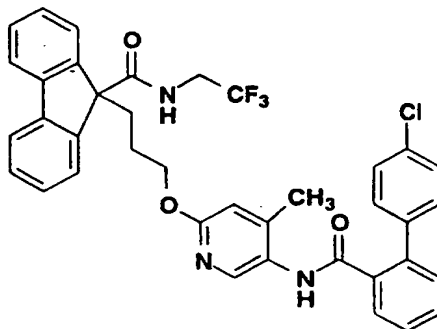


MS (ESI, + ion): 652 (M+H).

15

Example 467

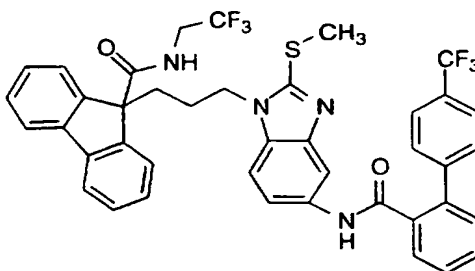
9-[3-[[5-[[[4'-Chloro[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



MS (ESI, + ion): 670 (M+H).

Example 468

5 9-[3-[2-(Methylthio)-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

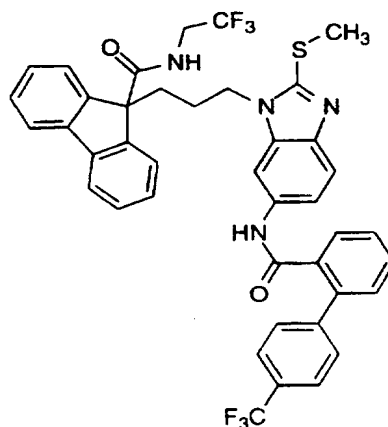


MS: (M+H)⁺ @ 759.

10

Example 469

9-[3-[2-(Methylthio)-6-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

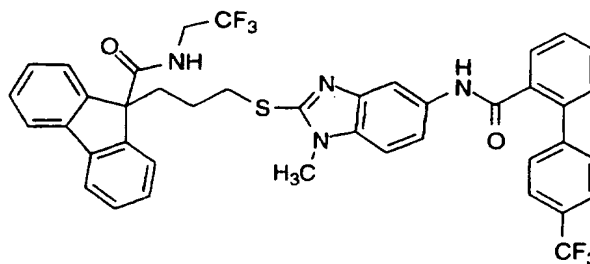


MS: (M+H)⁺ @ 759.

15

Example 470

9-[3-[[1-Methyl-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-2-yl]thio]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

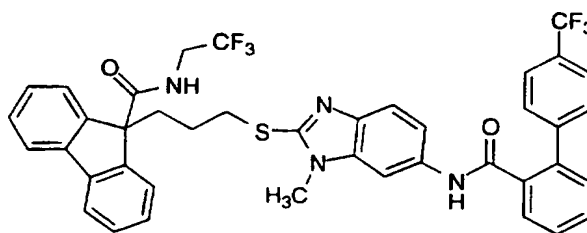


MS: (M+H)⁺ @ 759.

5

Example 471

9-[3-[[1-Methyl-6-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-2-yl]thio]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

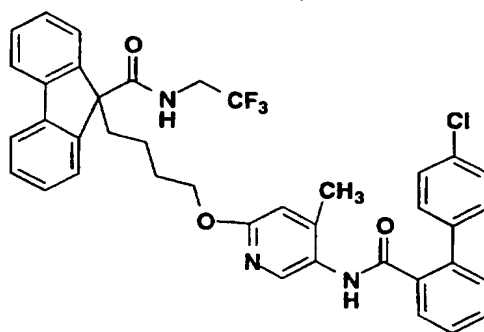


MS: (M+H)⁺ @ 759.

10

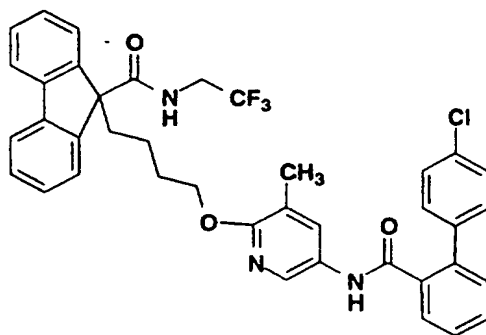
Example 472

9-[4-[[5-[[[4'-Chloro[1,1'-biphenyl]-2-yl]carbonyl]amino]-4-methyl-2-pyridinyloxy]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



MS (ESI, + ion): 684 (M+H).

15

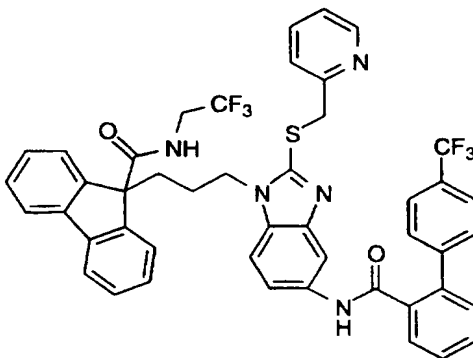
Example 473

MS (ESI, + ion): 684 (M+H).

5

Example 474

9-[3-[2-[(2-Pyridinylmethyl)thio]-5-[[[4'-(trifluoromethyl)][1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

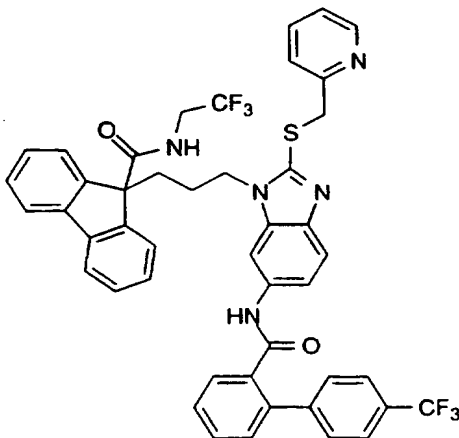


MS: (M+H)⁺ @ 836; (M-H)⁻ @ 834.

10

Example 475

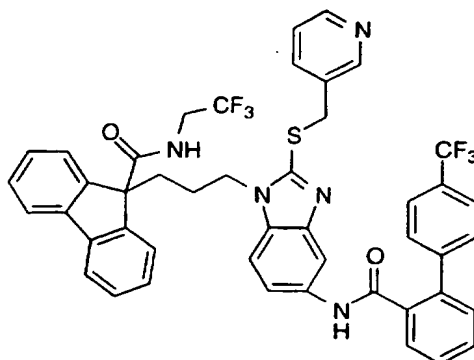
9-[3-[2-[(2-Pyridinylmethyl)thio]-6-[[[4'-(trifluoromethyl)][1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



MS: (M+H)⁺ @ 836; (M-H)⁻ @ 834.

Example 476

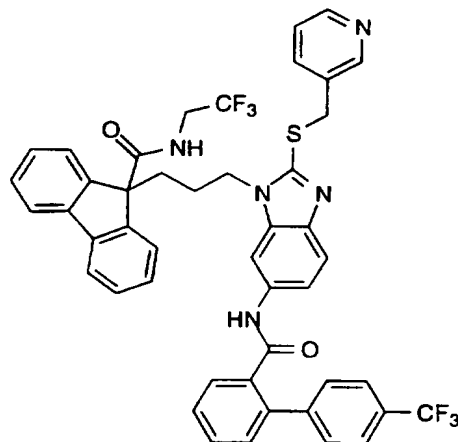
9-[3-[2-[(2-Pyridinylmethyl)thio]-6-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



5 MS: (M+H)⁺ @ 836; (M-H)⁻ @ 834.

Example 477

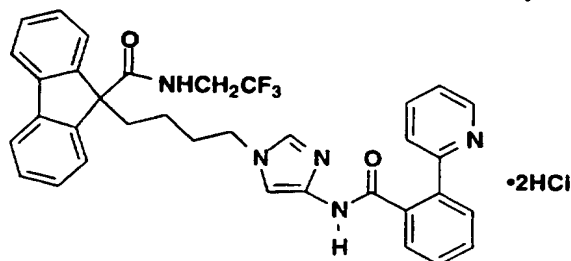
9-[3-[2-[(3-Pyridinylmethyl)thio]-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



10 MS: (M+H)⁺ @ 836; (M-H)⁻ @ 834.

Example 478

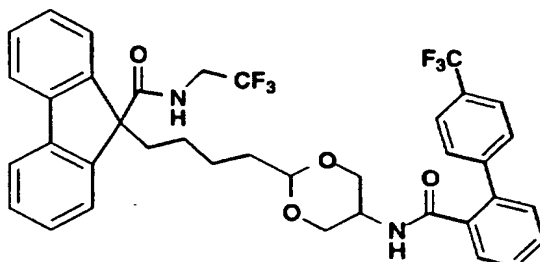
9-[4-[4-[[2-(2-Pyridinyl)benzoyl]amino]-1H-imidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.



MS: $(M+H)^+ = 610$.

Example 479

N-(2,2,2-Trifluoroethyl)-9-[4-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1,3-dioxan-2-yl]butyl]-9H-fluorene-9-carboxamide, isomer A.



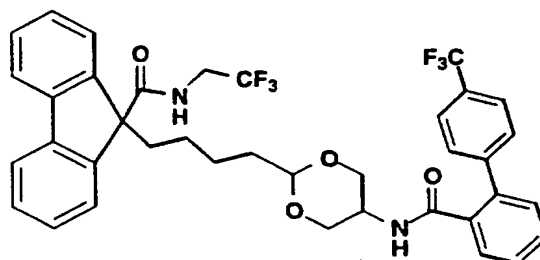
5

"Isomer A"

MS (electrospray, - ions) m/z 697 $(M+H)$.

Example 480

N-(2,2,2-Trifluoroethyl)-9-[4-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1,3-dioxan-2-yl]butyl]-9H-fluorene-9-carboxamide, isomer B.



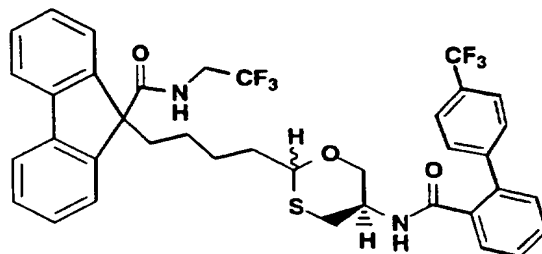
10

"Isomer B"

MS (electrospray, - ions) m/z 697 $(M+H)$.

Example 481

(5R)-N-(2,2,2-Trifluoroethyl)-9-[4-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1,3-oxathian-2-yl]butyl]-9H-fluorene-9-carboxamide, isomer A.



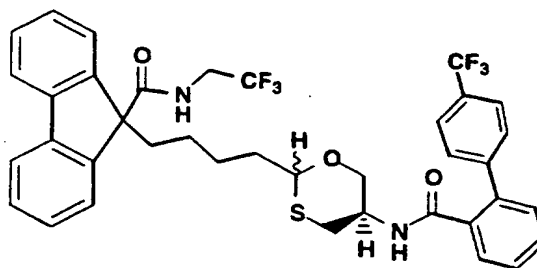
15

ISOMER A

MS (electrospray, - ions) m/z 713 $(M+H)$.

Example 482

(5R)-N-(2,2,2-Trifluoroethyl)-9-[4-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1,3-oxathian-2-yl]butyl]-9H-fluorene-9-carboxamide, isomer B.



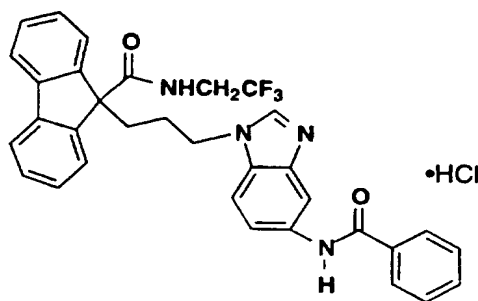
ISOMER B

MS (electrospray, - ions) m/z 713 ($M+H$).

5

Example 483

9-[3-[5-(Benzoylamino)-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

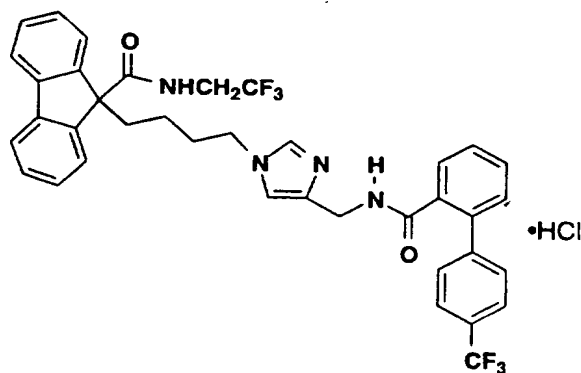


MS ($M+H$)⁺ = 569.

10

Example 484

N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]methyl]-1H-imidazol-1-yl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

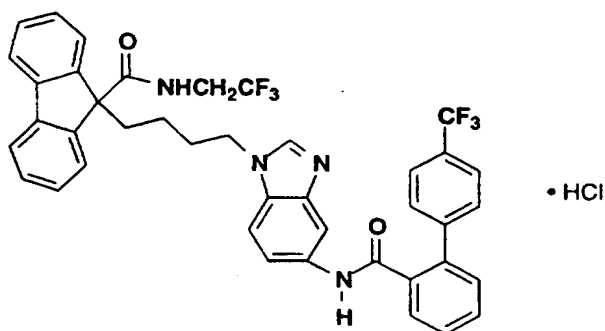


MS ($M+H$)⁺ = 691.

15

Example 485

N-(2,2,2-Trifluoroethyl)-9-[4-[5-[[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

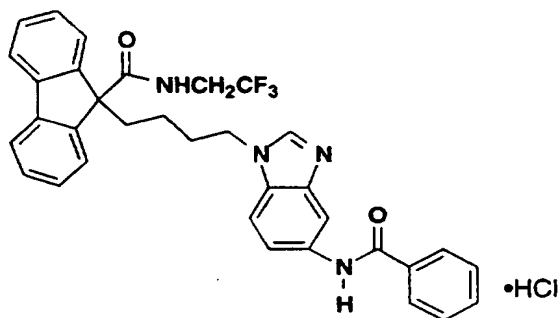


MS (M+H)⁺ = 727.

5

Example 486

9-[4-[5-(Benzoylamino)-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

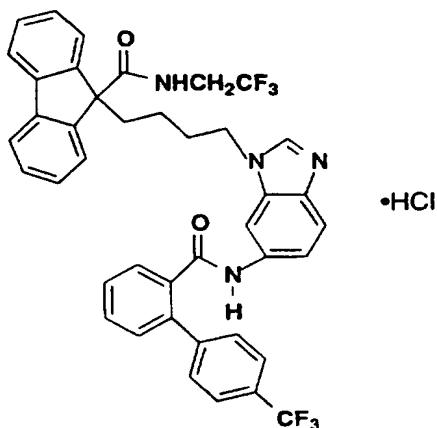


MS (M+H)⁺ = 583.

10

Example 487

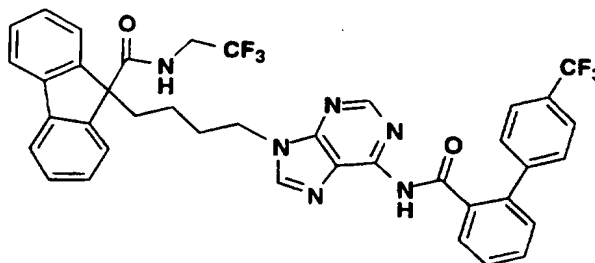
N-(2,2,2-Trifluoroethyl)-9-[4-[6-[[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.



MS (M+H)⁺ = 727.

Example 488

N-(2,2,2-Trifluoroethyl)-9-[4-[6-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-9H-purin-9-yl]butyl]-9H-fluorene-9-carboxamide.

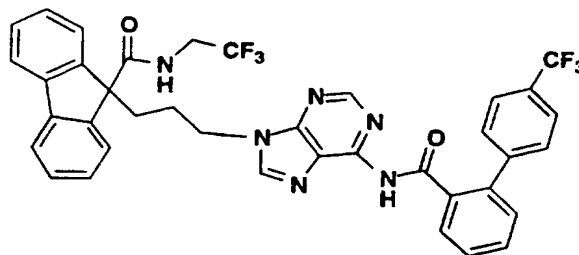


5

MS: (electrospray, + ions) m/z 729 (M+H).

Example 489

N-(2,2,2-Trifluoroethyl)-9-[3-[6-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-9H-purin-9-yl]propyl]-9H-fluorene-9-carboxamide.

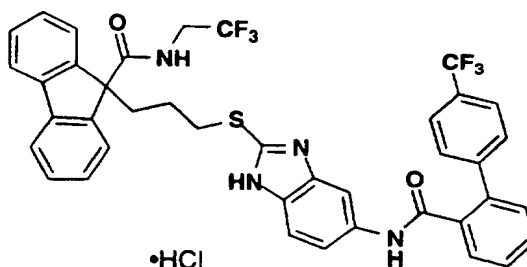


10

MS: (electrospray, + ions) m/z 715 (M+H).

Example 490

N-(2,2,2-Trifluoroethyl)-9-[3-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-2-yl]propyl]thio]-9H-fluorene-9-carboxamide, monohydrochloride.

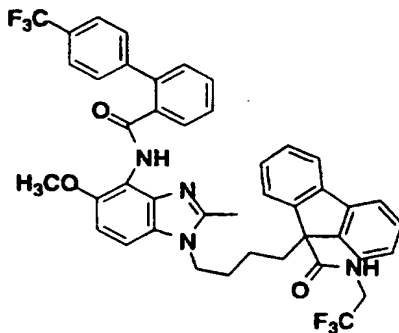


15

MS: (M+H)⁺ @ 745.

Example 491

9-[4-[5-Methoxy-2-methyl-4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

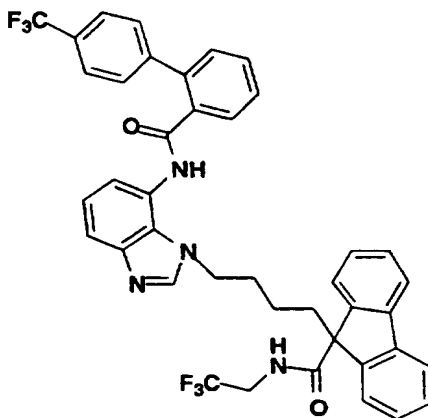


MS: (electrospray, + ions).

5

Example 492

N-(2,2,2-Trifluoroethyl)-9-[4-[7-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-9H-fluorene-9-carboxamide.

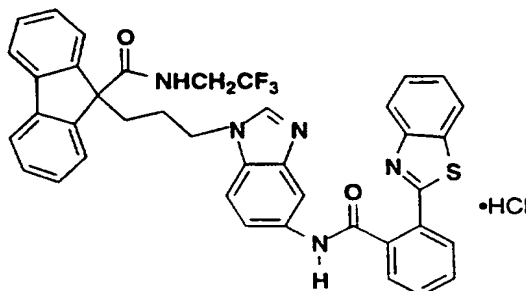


MS: (electrospray, + ions) m/z 727 (M+H).

10

Example 493

9-[3-[5-[[2-(2-Benzothiazolyl)benzoyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

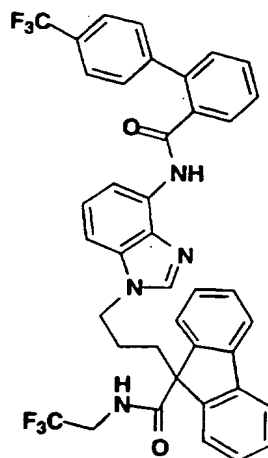


MS: (M+H)⁺ = 702.

15

Example 494

N-(2,2,2-Trifluoroethyl)-9-[3-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-9H-fluorene-9-carboxamide.

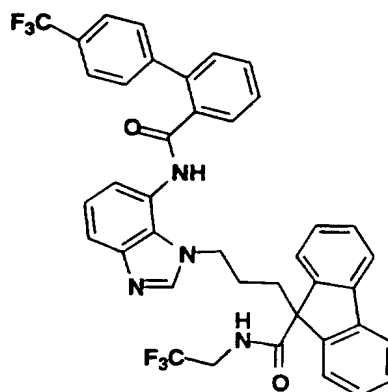


MS: (electrospray, + ions) m/z 713 (M+H).

5

Example 495

N-(2,2,2-Trifluoroethyl)-9-[3-[7-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-9H-fluorene-9-carboxamide.

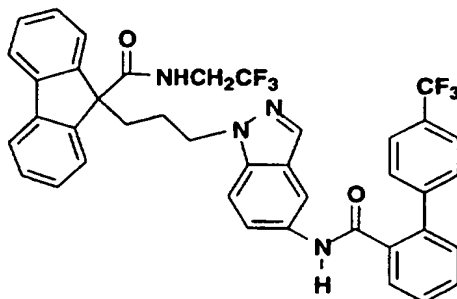


MS: (electrospray, + ions) m/z 713 (M+H).

10

Example 496

N-(2,2,2-Trifluoroethyl)-9-[3-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-indazol-1-yl]propyl]-9H-fluorene-9-carboxamide.

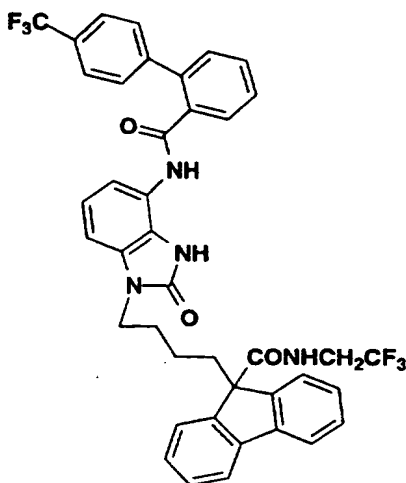


MS: $(M+H)^+ = 713$.

5

Example 497

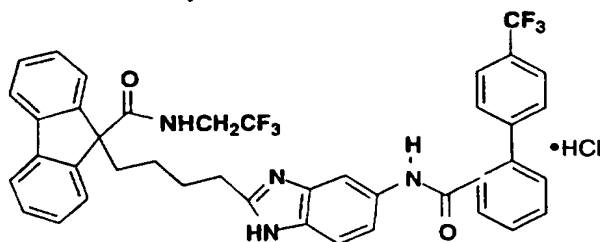
9-[4-[1,3-Dihydro-2-oxo-4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2H-benzimidazol-2-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



10 MS: (electrospray, + ions) m/z 743 $(M+H)^+$.

Example 498

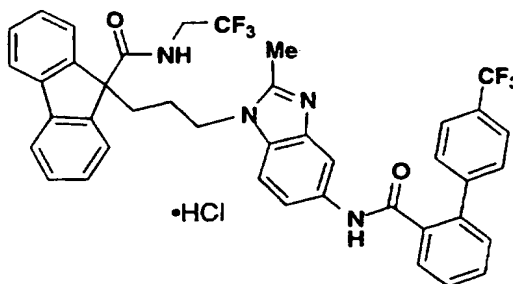
N-(2,2,2-Trifluoroethyl)-9-[4-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-2-yl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.



15 MS $(M+H)^+ = 727$.

Example 499

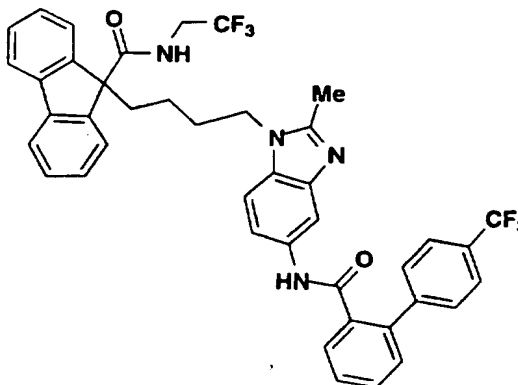
9-[3-[2-Methyl-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.



5 MS: (M)⁺ @ 726.

Example 500

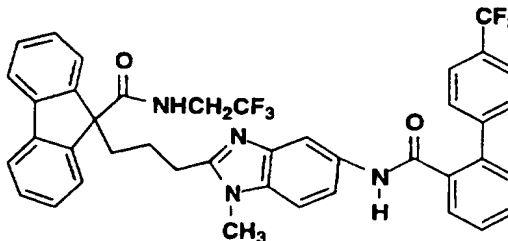
9-[4-[2-Methyl-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



10 MS: (M)⁺.

Example 501

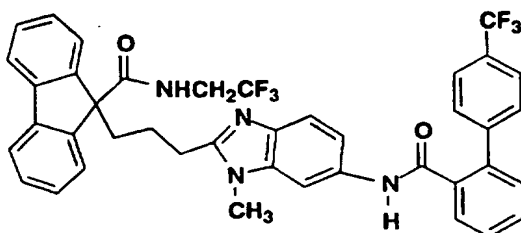
9-[3-[1-Methyl-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-2-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



15 MS (M+H)⁺ = 727.

Example 502

9-[3-[1-Methyl-6-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-2-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

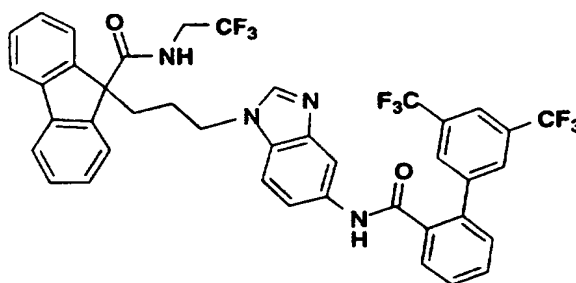


MS (M+H)⁺ = 727.

5

Example 503

9-[3-[5-[[[3',5'-Bis(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

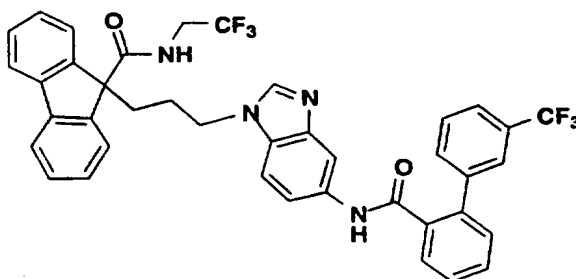


MS: (M)⁺ @ 780.

10

Example 504

N-(2,2,2-Trifluoroethyl)-9-[3-[5-[[[3'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-9H-fluorene-9-carboxamide.

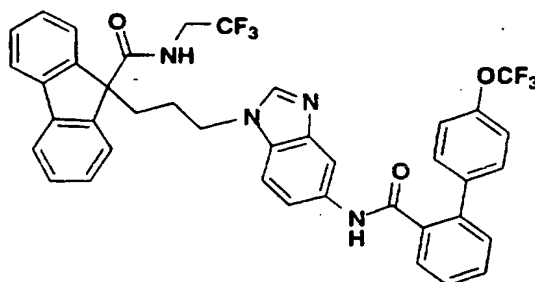


MS: (M)⁺ @ 712.

15

Example 505

N-(2,2,2-Trifluoroethyl)-9-[3-[5-[[[4'-(trifluoromethoxy)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-9H-fluorene-9-carboxamide.

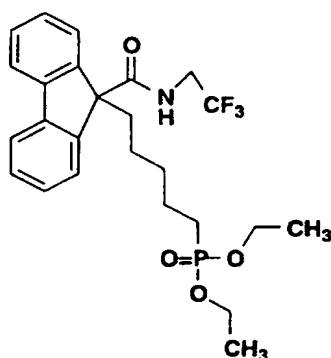


MS: (M)⁺ @ 728.

Example 506

5

9-[[5-(Diethoxyphosphinyl)pentyl]amino]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

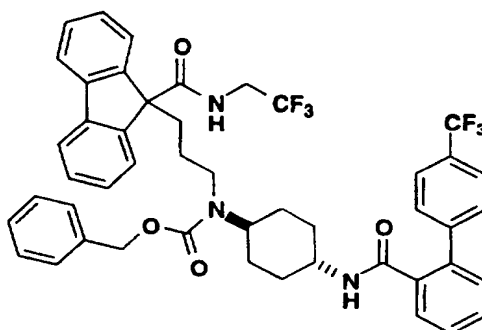


MS (ESI, + ions): 498 (M+H), 515 (M+NH₄).

Example 507

10

trans-[3-[9-[[2,2,2-Trifluoroethyl]amino]carbonyl]-9H-fluorene-9-yl]propyl[[4-[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]cyclohexyl]carbamic acid, phenylmethyl ester.



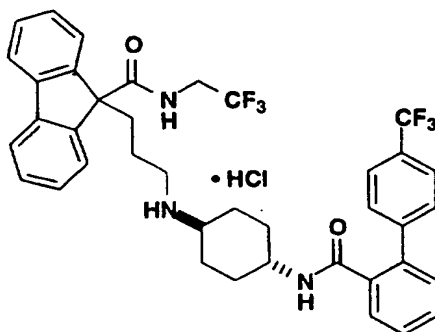
trans isomer

MS (ES, + ions) m/z 845 [M+NH₄].

Example 508

15

trans-N-(2,2,2-Trifluoroethyl)-9-[3-[[4-[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]cyclohexyl]amino]propyl]-9H-fluorene-9-carboxamide, monohydrochloride.



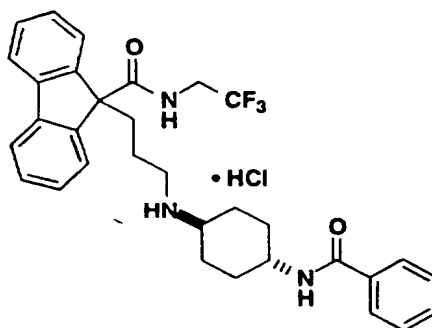
trans isomer

MS (ES, + ions) m/z 694 (M+H).

Example 509

trans-9-[3-[[4-(Benzoylamino)cyclohexyl]amino]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

5

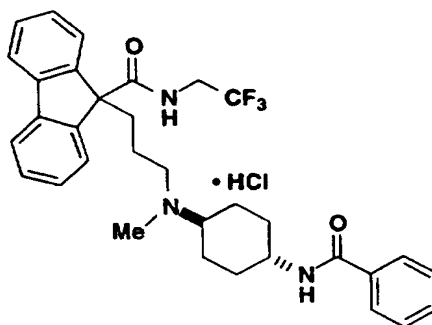


MS (ES, + ions) m/z 550 [M+H].

Example 510

trans-9-[3-[[4-(Benzoylamino)cyclohexyl]methylamino]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

10

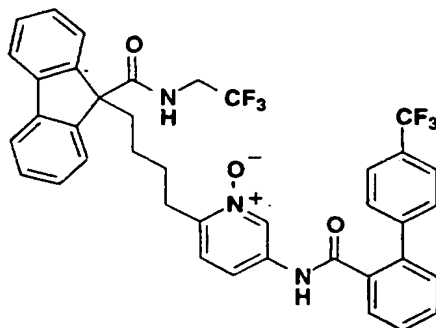


MS (ES, + ions) m/z 647 [M+H].

Example 511

N-(2,2,2-Trifluoroethyl)-9-[4-[5-[[[4'-(trifluoromethyl)][1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]butyl]-9H-fluorene-9-carboxamide, N-oxide.

15

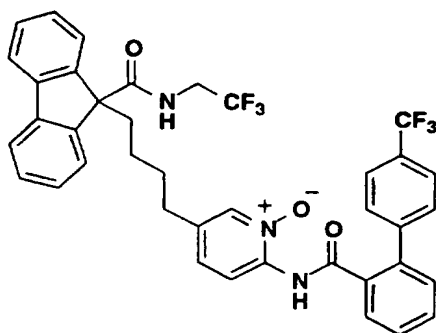


MS (ES, + ions) m/z 704 [M+H].

Example 512

N-(2,2,2-Trifluoroethyl)-9-[4-{2-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-5-pyridinyl]butyl]-9H-fluorene-9-carboxamide, N-oxide.

5

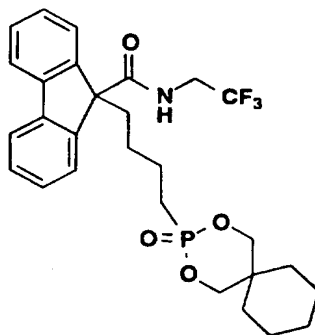


MS (ES, + ions) m/z 704 [M+H].

Example 513

9-[4-(3-Oxo-2,4-dioxo-3-phosphaspiro[5.5]undecan-3-yl)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

10

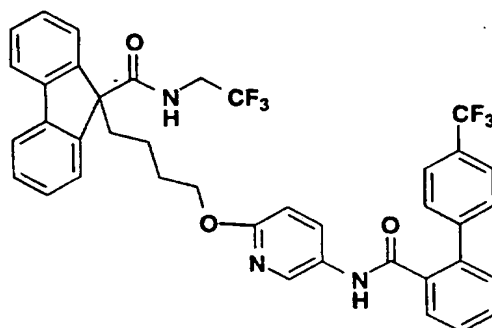


MS (ESI, + ion): 536 (M+H).

Example 514

N-(2,2,2-Trifluoroethyl)-9-[4-{[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]oxy]butyl]-9H-fluorene-9-carboxamide.

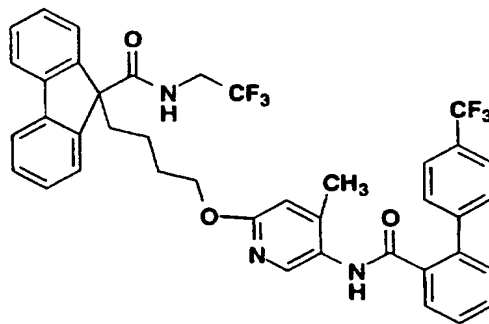
15



MS (ESI, + ion): 704 (M+H).

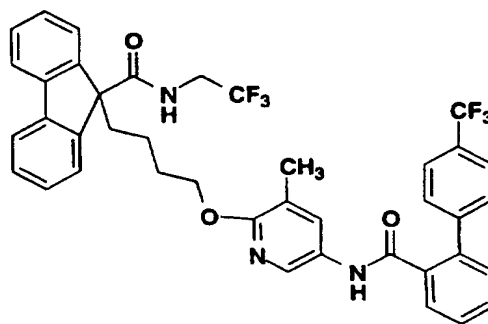
Example 515

5 9-[4-[[4-Methyl-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]oxy]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



MS (ESI, + ion): 718 (M+H).

Example 516

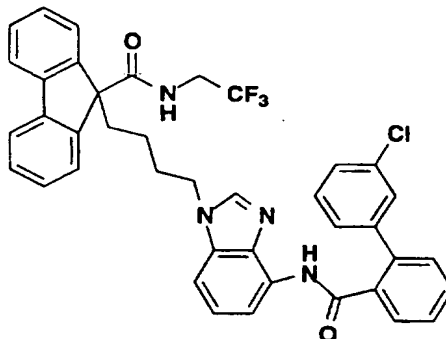


10

MS (ESI, + ion): 718 (M+H).

Example 517

9-[4-[4-[(3'-Chloro[1,1'-biphenyl]-2-yl)carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

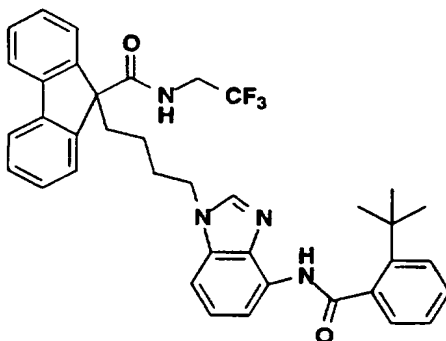


MS (ESI, + ion): 693 (M+H).

5

Example 518

9-[4-[4-[2-(1,1-Dimethylethyl)benzoyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

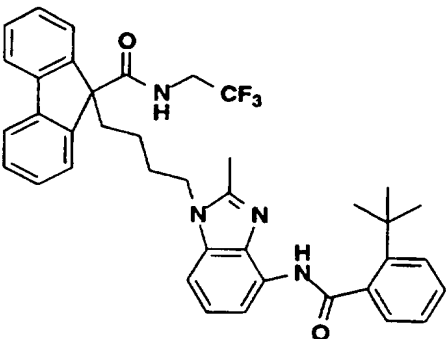


MS (ESI, + ion): 639 (M+H).

10

Example 519

9-[4-[4-[2-(1,1-Dimethylethyl)benzoyl]amino]-2-methyl-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

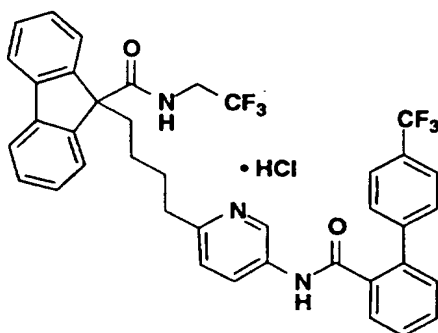


MS (ESI, + ion): (M+H).

15

Example 520

N-(2,2,2-Trifluoroethyl)-9-[4-[5-[[[4'-(trifluoromethyl)(1,1'-biphenyl)-2-yl]carbonyl]amino]-2-pyridinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

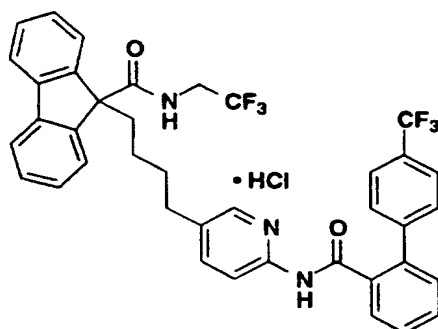


MS (ES, + ions) m/z 688 [M+H].

5

Example 521

N-(2,2,2-Trifluoroethyl)-9-[4-[2-[[[4'-(trifluoromethyl)(1,1'-biphenyl)-2-yl]carbonyl]amino]-5-pyridinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

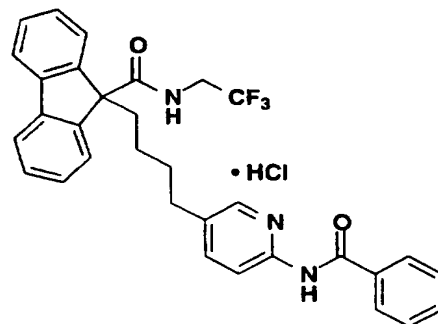


MS (ES, + ions) m/z 688 [M+H].

10

Example 522

9-[4-[2-(Benzoylamino)-5-pyridinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

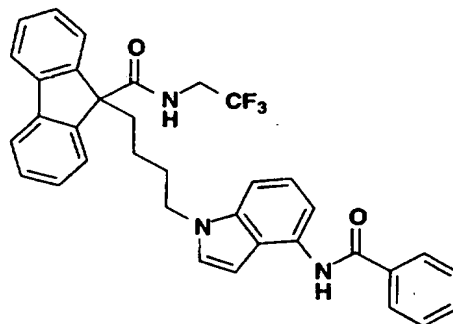


MS (ES, + ions) m/z 544 [M+H].

15

Example 523

9-[4-[4-(Benzoylamino)-1H-indol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

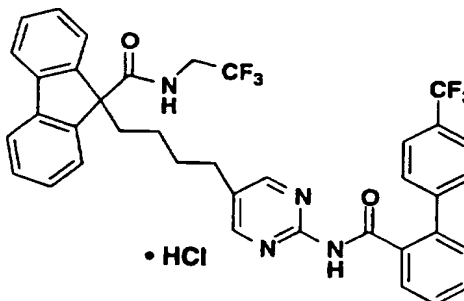


MS (ES, + ions) m/z 582 [M+H].

5

Example 524

N-(2,2,2-Trifluoroethyl)-9-[4-[2-[[4'-(trifluoromethyl)][1,1'-biphenyl]-2-yl]carbonyl]amino]-5-pyrimidinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

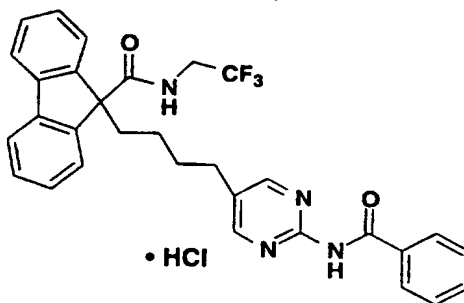


MS (ES, + ions) m/z 689 (M+H).

10

Example 525

9-[4-[2-(Benzoylamino)-5-pyrimidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

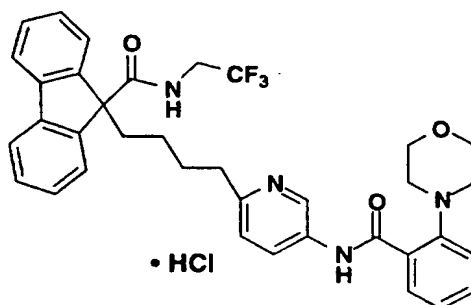


MS (ES, + ions) m/z 545 (M+H).

15

Example 526

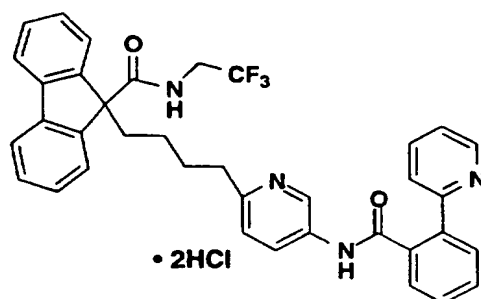
9-[4-[5-[[2-(4-Morpholinyl)benzoyl]amino]-2-pyridinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.



5 MS (ES, + ions) m/z 629 (M+H).

Example 527

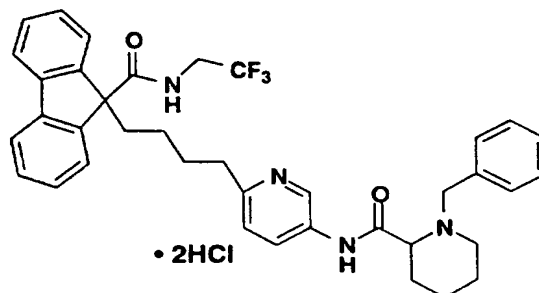
9-[4-[5-[[2-(2-Pyridinyl)benzoyl]amino]-2-pyridinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.



10 MS (ES, + ions) m/z 621 (M+H).

Example 528

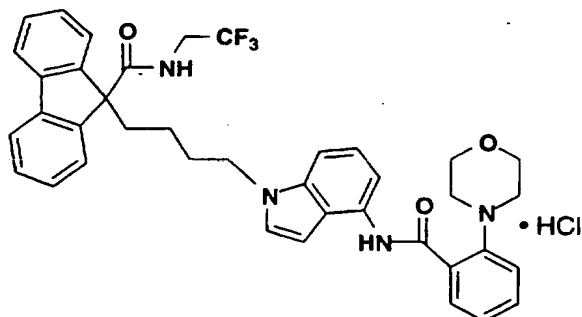
9-[4-[5-[[[1-(Phenylmethyl)-2-piperidinyl]carbonyl]amino]-2-pyridinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.



15 MS (ES, + ions) m/z 641 (M+H).

Example 529

9-[4-[4-[[2-(4-Morpholinyl)benzoyl]amino]-1H-indol-1-yl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

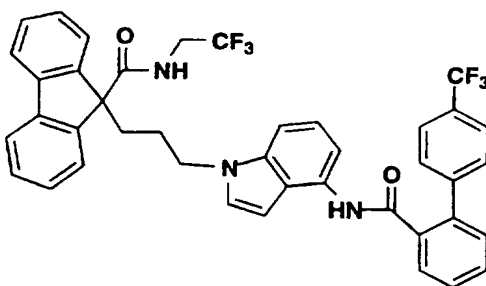


MS (ES, + ions) m/z 536 (M+H).

Example 530

N-(2,2,2-Trifluoroethyl)-9-[3-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-indol-1-yl]propyl]-9H-fluorene-9-carboxamide.

5

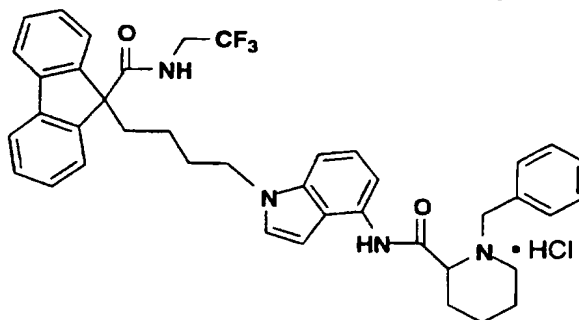


MS (ES, + ions) m/z 729 (M+ NH₄).

Example 531

N-[1-[4-[9-[(2,2,2-trifluoroethyl)carbonyl]amino]-9H-fluoren-9-yl]butyl]-1H-indol-4-yl]-1-(phenylmethyl)-2-piperidinecarboxamide, monohydrochloride.

10

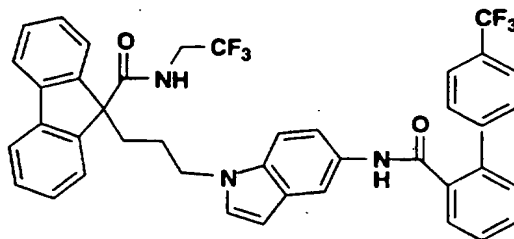


MS (ES, + ions) m/z 679 (M+H).

Example 532

N-(2,2,2-Trifluoroethyl)-9-[3-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-indol-5-yl]propyl]-9H-fluorene-9-carboxamide.

15

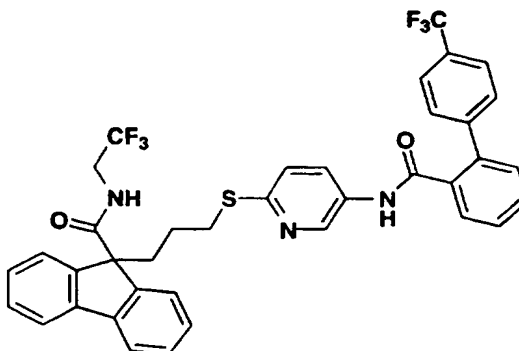


MS (ES, + ions) m/z 729 ($M+NH_4$).

Example 533

N-(2,2,2-Trifluoroethyl)-9-[3-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]thio]propyl]-9H-fluorene-9-carboxamide.

5

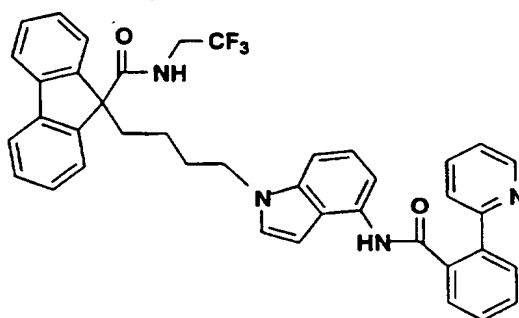


MS (ES, + ions) m/z @ 706 [$M+H$] $^+$.

Example 534

9-[4-[4-[[2-(2-Pyridinyl)benzoyl]amino]-1H-indol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

10

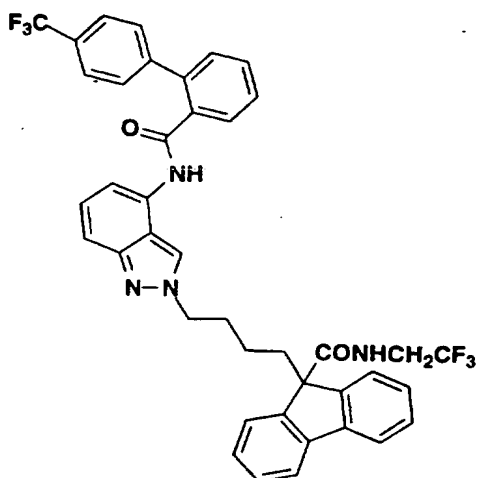


MS (ES, + ions) m/z 659 ($M+H$).

Example 535

N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2H-indazol-2-yl]butyl]-9H-fluorene-9-carboxamide.

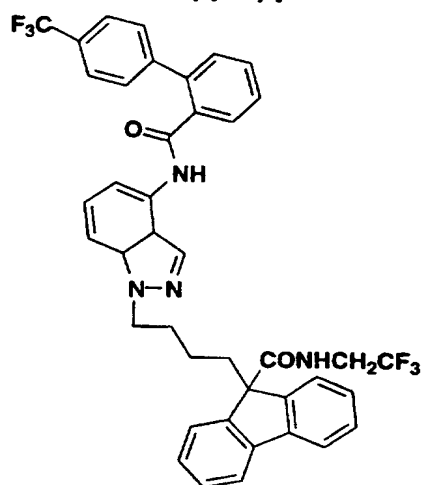
15



MS: (electrospray, + ions) m/z 727 (M+H).

Example 536

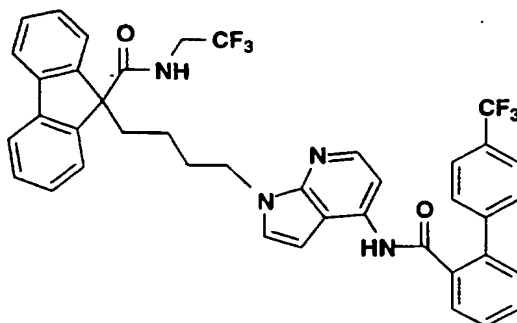
5 N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-indazol-1-yl]butyl]-9H-fluorene-9-carboxamide.



MS: (electrospray, + ions) m/z 727 (M+H).

Example 537

10 N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-pyrrolo[2,3-b]pyridin-1-yl]butyl]-9H-fluorene-9-carboxamide.

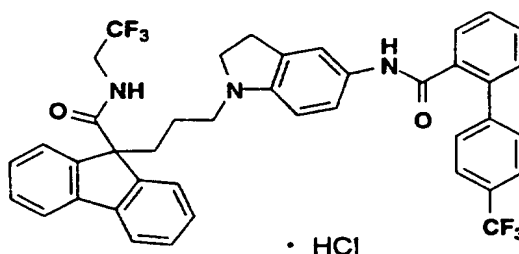


MS (ES, + ions) m/z 727 (M+H).

Example 538

9-[3-[2,3-Dihydro-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-indol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

5

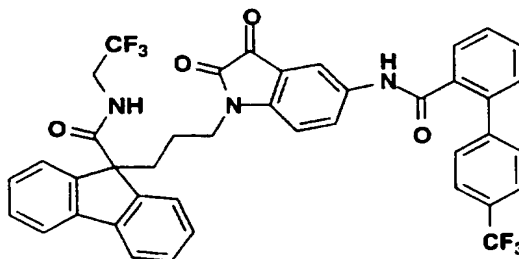


MS (ESI) m/z [M+H]⁺ @ 714, [M+H] @ 712.

Example 539

9-[3-[2,3-Dihydro-2,3-dioxo-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-indol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

10

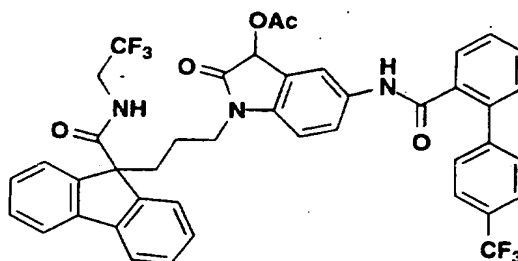


MS [M+H]⁺ @ 742, [M-H]⁻ @ 740, (ESI).

Example 540

9-[3-[3-(Acetyloxy)-2,3-dihydro-2-oxo-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-indol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

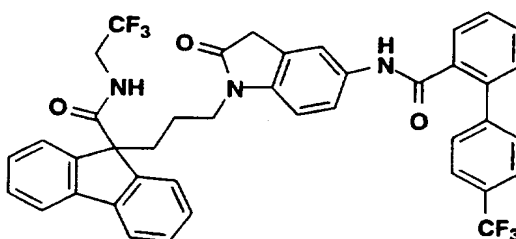
15



MS $[M+H]^+$ @ 786, $[M-H]^-$ @ 784, (ESI).

Example 541

5 9-[3-[2,3-Dihydro-2-oxo-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-indol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

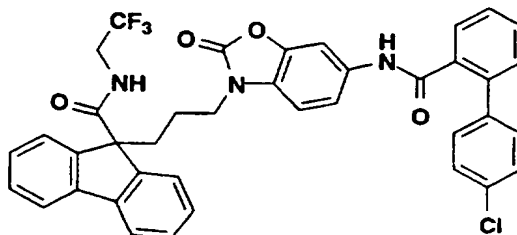


MS: m/z $[M+H]^+$ @ 728, $[M-H]^-$ @ 726, (ESI).

10

Example 542

9-[3-[6-[[[4'-Chloro[1,1'-biphenyl]-2-yl]carbonyl]amino]-2,3-dihydro-2-oxo-3-benzoxazolyl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

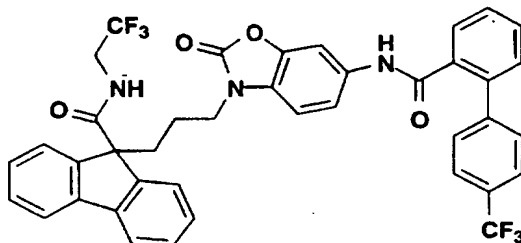


MS: m/z @ 713 $[M+NH_4]^+$, @ 694 $[M-H]^-$, (ESI).

15

Example 543

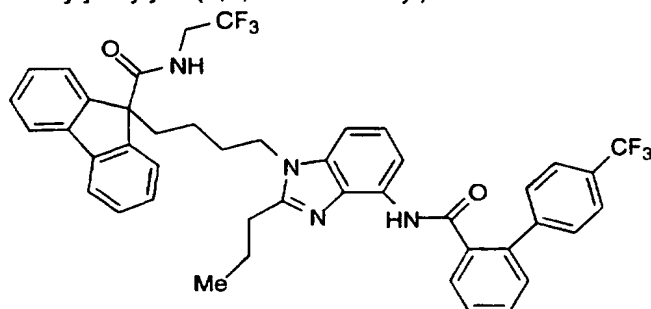
9-[3-[2,3-Dihydro-2-oxo-6-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-3-benzoxazolyl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



MS: m/z $[M+H]^+$ @ 730, $[M-H]^-$ @ 728, (ESI).

Example 544

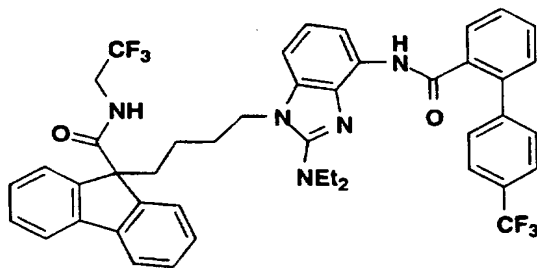
5 9-[4-[2-Propyl-4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



MS: m/z $[M+H]^+$ 769; $[M-H]^-$ 767.

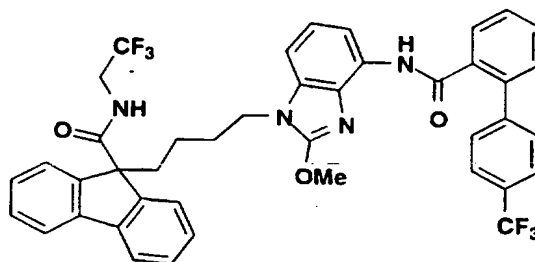
Example 545

10 9-[4-[2-(Diethylamino)-4-[[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

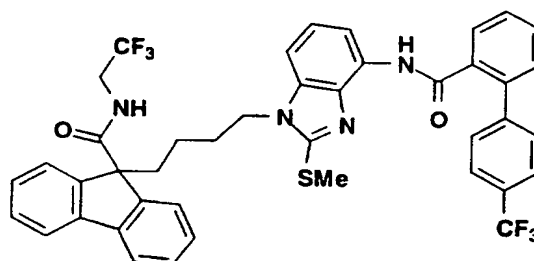


Example 546

9-[4-[2-Methoxy-4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

Example 547

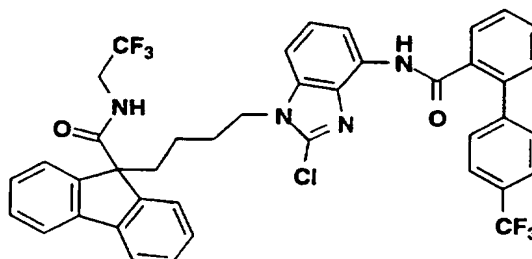
9-[4-[2-(Methylthio)-4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



5

Example 548

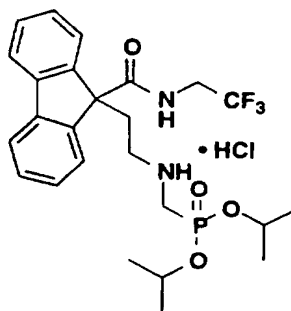
9-[4-[2-Chloro-4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



10

Example 549

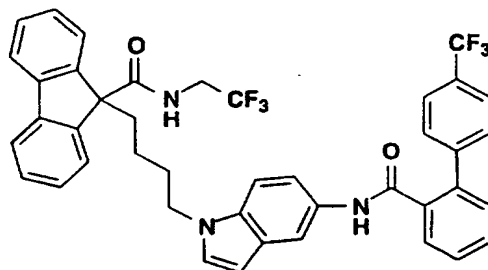
[[2-[9-[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]ethyl]amino]methyl]phosphonic acid, bis(1-methylethyl) ester.



MS (ES, + ions) m/z 513 [M+H].

Example 550

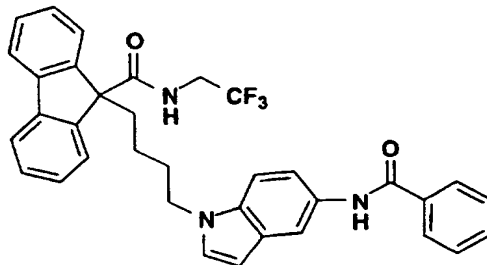
N-(2,2,2-Trifluoroethyl)-9-[4-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-indol-1-yl]butyl]-9H-fluorene-9-carboxamide.



5 MS (ES, + ions) m/z 726 [M+H].

Example 551

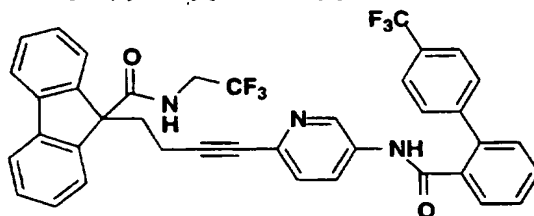
9-[4-[5-(Benzoylamino)-1H-indol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



10 MS (ES, + ions) m/z 582 [M+H].

Example 552

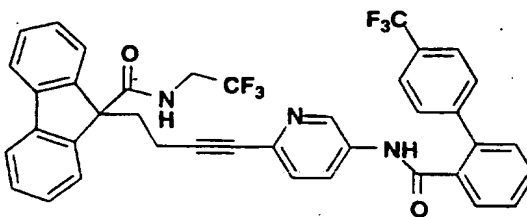
N-(2,2,2-Trifluoroethyl)-9-[4-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]-3-butenyl]-9H-fluorene-9-carboxamide.



15 MS (ES, + ions) m/z 684 (M+H).

Example 552A

N-(2,2,2-Trifluoroethyl)-9-[4-[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]-3-butenyl]-9H-fluorene-9-carboxamide, trifluoroacetate.

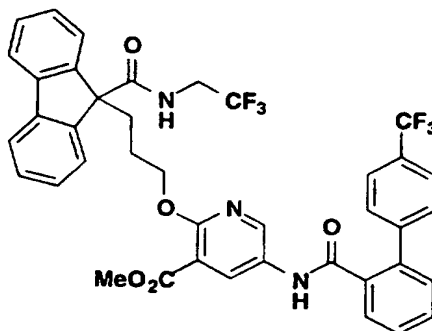


•TFA

MS (ES, + ions) m/z 684 (M+H).

Example 553

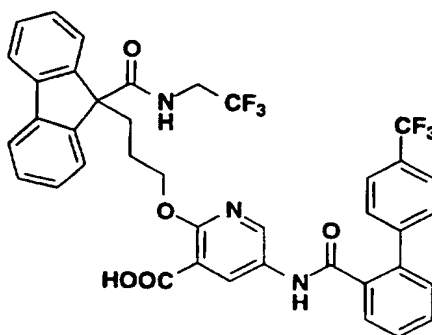
2-[3-[9-[[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]propoxy]-5-
 5 [[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-3-pyridinecarboxylic
 acid, methyl ester.



MS (ES, + ions) m/z 748 [M+H].

Example 554

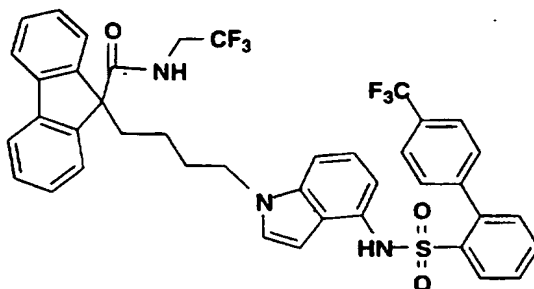
2-[3-[9-[[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]propoxy]-5-
 10 [[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-3-pyridinecarboxylic
 acid.



MS (ES, + ions) m/z 734 [M+H].

Example 555

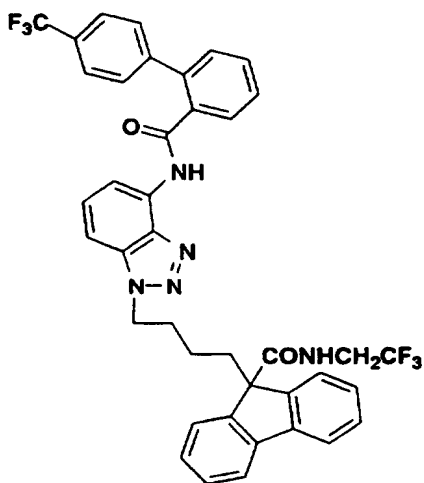
N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-
 15 2-yl]sulfonyl]amino]-1H-indol-1-yl]butyl]-9H-fluorene-9-carboxamide.



MS (ES, + ions) m/z 762 (M+H).

Example 556

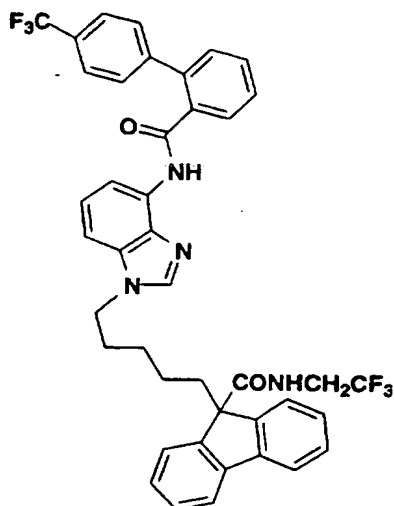
5 N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzotriazol-1-yl]butyl]-9H-fluorene-9-carboxamide.



MS: (electrospray, + ions) m/z 728 (M+H).

Example 557

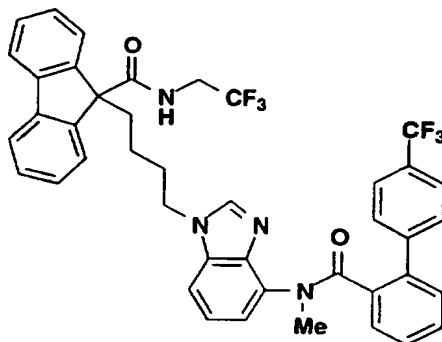
10 N-(2,2,2-Trifluoroethyl)-9-[5-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]pentyl]-9H-fluorene-9-carboxamide.



MS: (electrospray, + ions) m/z 741 (M+H).

Example 558

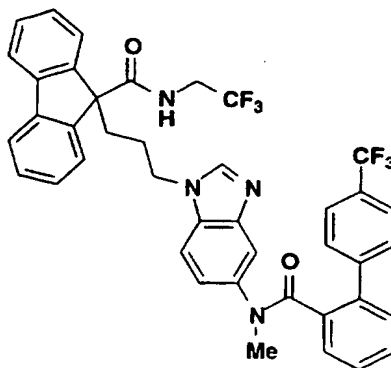
5 9-[4-[4-[Methyl[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



MS (ES, + ions) m/z 741 [M+H].

Example 559

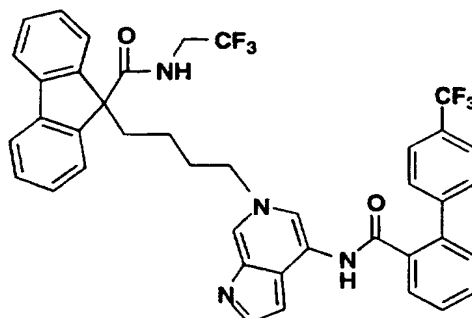
10 9-[3-[5-[Methyl[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



MS (ES, + ions) m/z 727 [M+H].

Example 560

N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-6H-pyrrolo[2,3-c]pyridin-6-yl]butyl]-9H-fluorene-9-carboxamide.

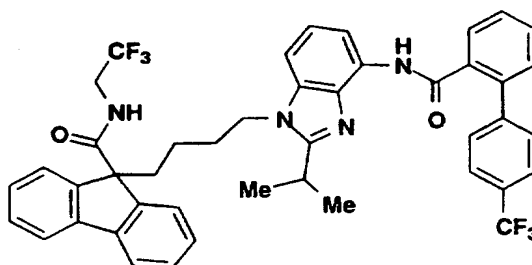


5

MS (ES, + ions) m/z 727 (M+H).

Example 561

9-[4-[2-(1-Methylethyl)-4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



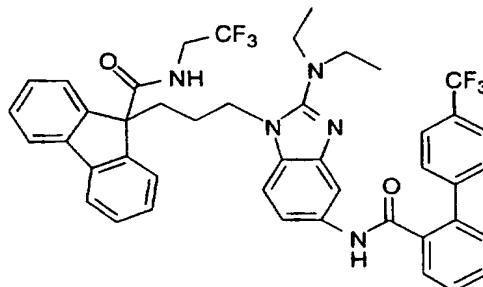
10

MS: m/z 769 (M+H)+.

Example 562

9-[3-[2-(Diethylamino)-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

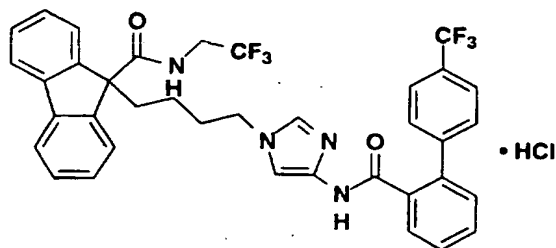
15



MS: (M+H)+. @ 784.

Example 563

N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-imidazol-1-yl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

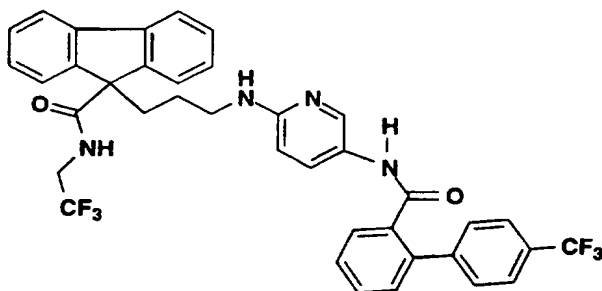


MS: (M+H)⁺ = 677.

5

Example 564

N-(2,2,2-Trifluoroethyl)-9-[3-[[[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]amino]propyl]-9H-fluorene-9-carboxamide, trifluoroacetate.



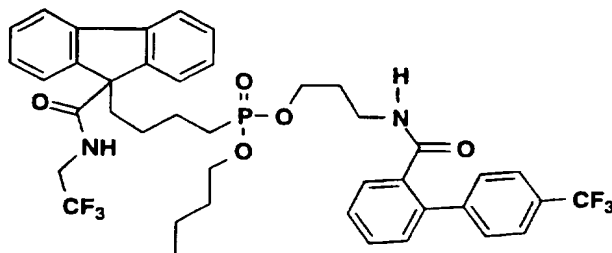
CF₃COOH Salt

MS (ES, NH₃, + ions) m/z 689 (M+H).

10

Example 565

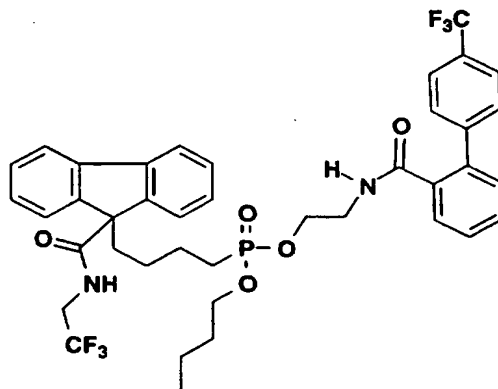
[4-[9-[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluorene-9-yl]butyl]phosphonic acid, butyl 3-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]propyl ester.



15 MS (ES, NH₃, + ions) m/z 806 (M+NH₄), 789 (M+H).

Example 566

[4-[9-[[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]butyl]phosphonic acid, butyl 2-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]ethyl ester.

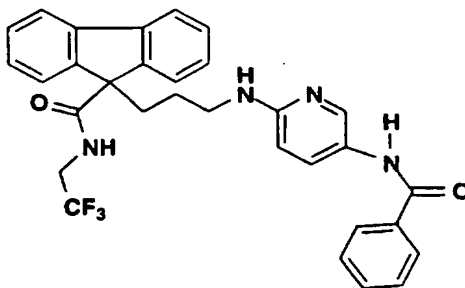


MS (ES, NH₃, + ions) m/z 792 (M+NH₄), 775 (M+H).

5

Example 567

9-[3-[[5-(Benzoylamino)-2-pyridinyl]amino]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.



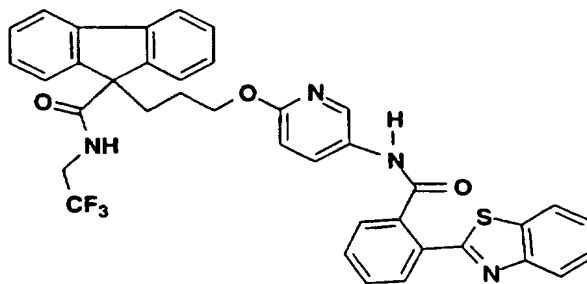
HCl Salt

MS (ES, NH₃, + ions) m/z 545 (M+H).

10

Example 568

9-[3-[[5-[[2-(2-Benzothiazolyl)benzoyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.



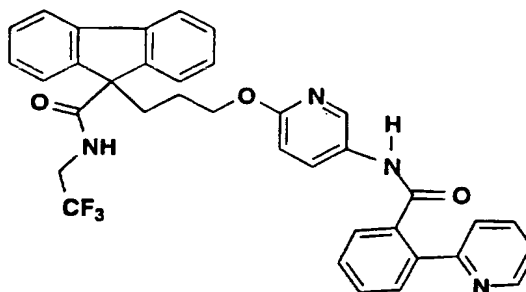
HCl Salt

MS (ES, NH₃, + ions) m/z 679 (M+H).

15

Example 569

9-[3-[[5-[[2-(2-Pyridinyl)benzoyl]amino]-2-pyridinyl]oxy]propyl]-
N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.



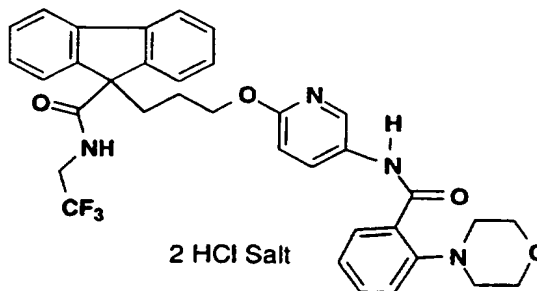
2 HCl Salt

MS (ES, NH₃, + ions) m/z 623 (M+H).

5

Example 570

9-[3-[[5-[[2-(4-Morpholinyl)benzoyl]amino]-2-pyridinyl]oxy]propyl]-
N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.



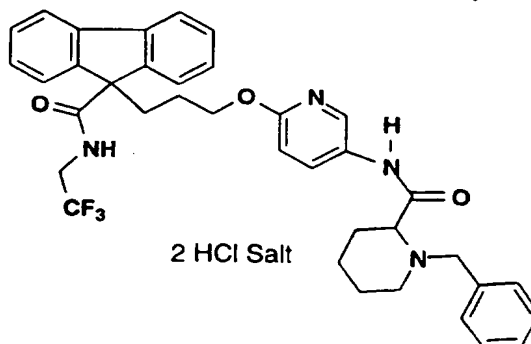
2 HCl Salt

MS (ES, NH₃, + ions) m/z 631 (M+H).

10

Example 571

1-(Phenylmethyl)-N-[2-[3-[9-[[2,2,2-trifluoroethyl]amino]carbonyl]-9H-fluoren-
9-yl]propoxy]-5-pyridinyl]-2-piperidinecarboxamide, dihydrochloride.



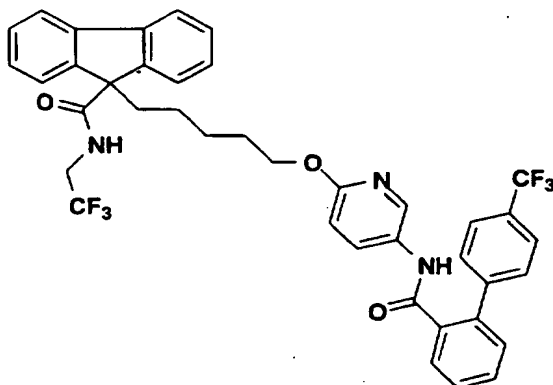
2 HCl Salt

MS (ES, NH₃, + ions) m/z 643 (M+H).

15

Example 572

N-(2,2,2-Trifluoroethyl)-9-[5-[[5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-
yl]carbonyl]amino]-2-pyridinyl]oxy]pentyl]-9H-fluorene-9-carboxamide.

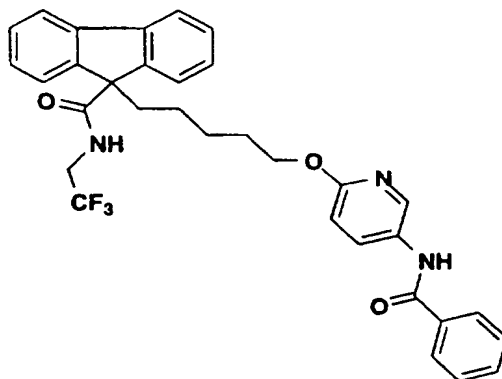


MS (ES, NH₃, + ions) m/z 718 (M+H).

Example 573

5

9-[5-[[5-(Benzoylamino)-2-pyridinyl]oxy]pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

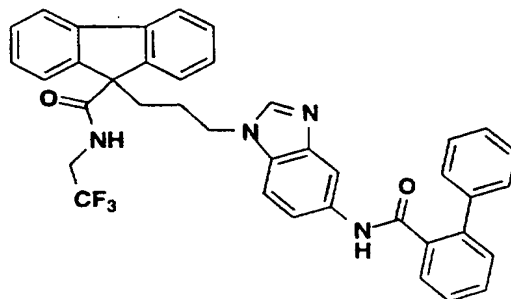


MS (ES, NH₃, + ions) m/z 574 (M+H).

Example 574

10

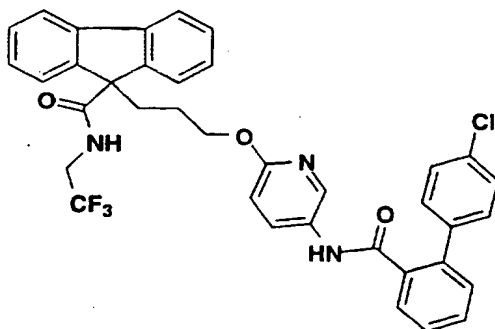
9-[3-[5-[[[4'-Chloro[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



MS (ES, NH₃, + ions) m/z 680 (M+H).

Example 575

9-[3-[[5-[[[4'-Chloro[1,1'-biphenyl]-2-yl]carbonyl]amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, hydrochloride.

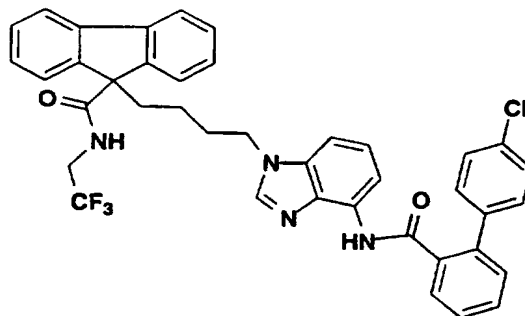


MS (ES, NH₃, + ions) m/z 656 (M).

5

Example 576

9-[4-[4-[[[4'-Chloro[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

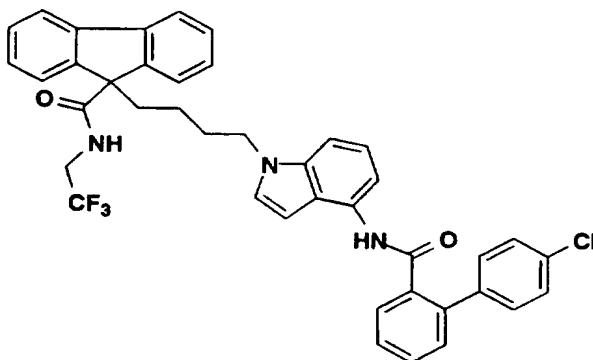


MS (ES, NH₃, + ions) m/z 693 (M).

10

Example 577

9-[4-[4-[[[4'-Chloro[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-indol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

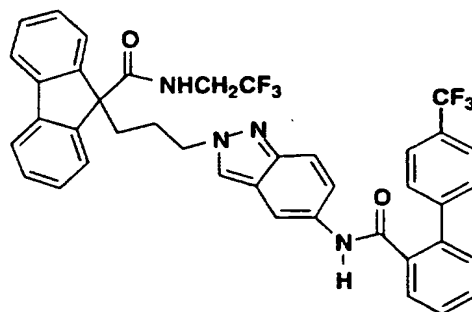


MS (ES, NH₃, + ions) m/z 692 (M).

15

Example 578

N-(2,2,2-Trifluoroethyl)-9-[3-[5-[[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-2H-indazol-2-yl]propyl]-9H-fluorene-9-carboxamide.

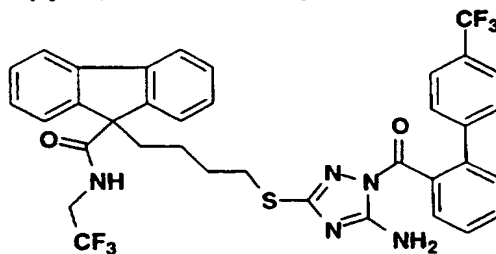


MS (M+H)⁺ = 713.

5

Example 579

9-[4-[[5-Amino-1-[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]-1H-1,2,4-triazol-3-yl]thio]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

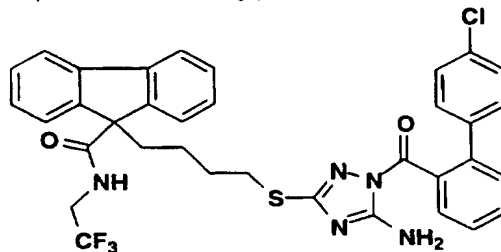


MS (ES, NH₃, + ions) m/z 710 (M+H).

10

Example 580

9-[4-[[5-Amino-1-[(4'-chloro[1,1'-biphenyl]-2-yl)carbonyl]-1H-1,2,4-triazol-3-yl]thio]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

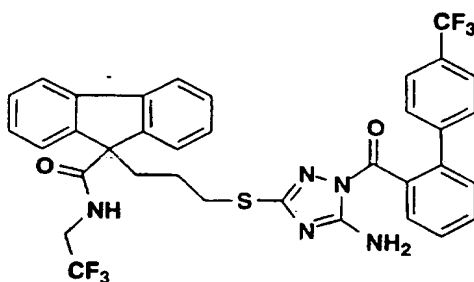


MS (ES, NH₃, + ions) m/z 676 (M+H).

15

Example 581

9-[3-[[5-Amino-1-[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]-1H-1,2,4-triazol-3-yl]thio]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

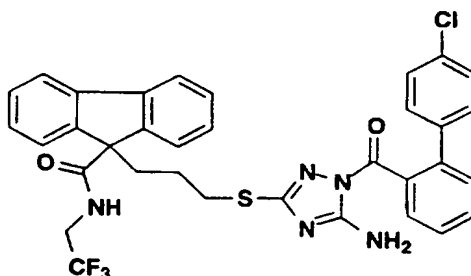


MS (ES, NH₃, + ions) m/z 696 (M+H).

Example 582

5

9-[3-[[5-Amino-1-[(4'-chloro[1,1'-biphenyl]-2-yl)carbonyl]-1H-1,2,4-triazol-3-yl]thio]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

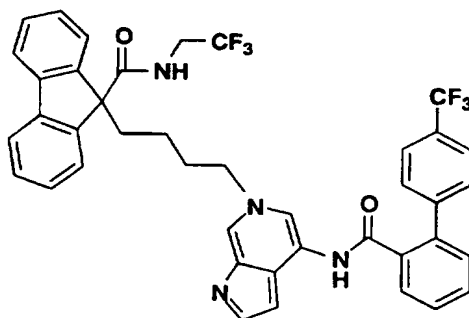


MS (ES, NH₃, + ions) m/z 662 (M+H).

Example 583

10

N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-6H-pyrrolo[2,3-c]pyridin-6-yl]butyl]-9H-fluorene-9-carboxamide.

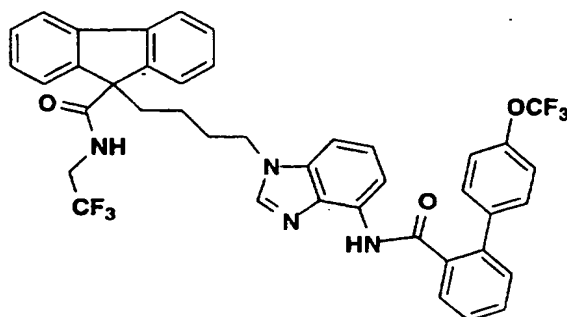


MS (ES, + ions) m/z 727 (M+H).

Example 584

15

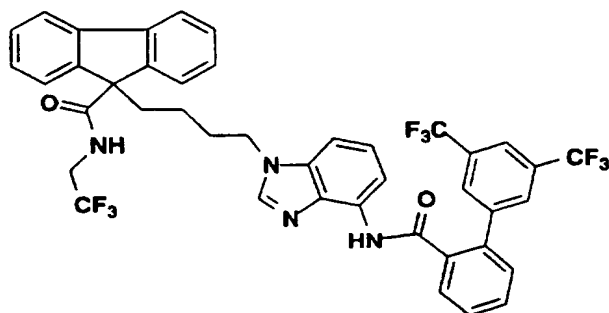
N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethoxy)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-9H-fluorene-9-carboxamide.



MS (ES, NH₃, + ions) m/z 743 (M+H).

Example 585

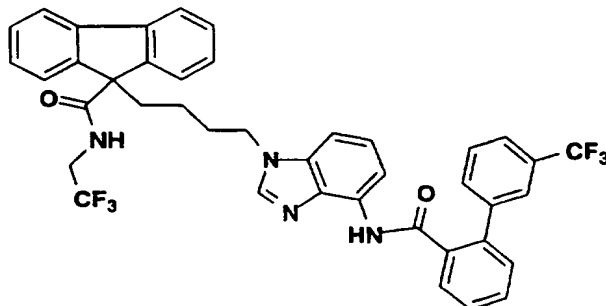
5 9-[4-[4-[[[3',5'-Bis(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.



MS (ES, NH₃, + ions) m/z 795 (M+H).

Example 586

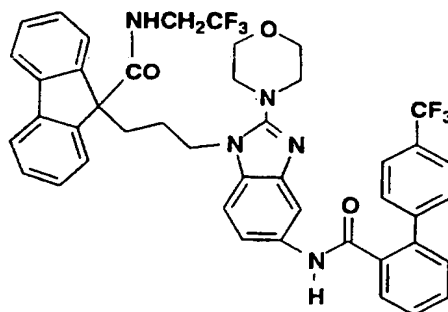
10 N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[3'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-9H-fluorene-9-carboxamide.



MS (ES, NH₃, + ions) m/z 727 (M+H).

Example 587

9-[3-[2-(4-Morpholinyl)-5-[[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

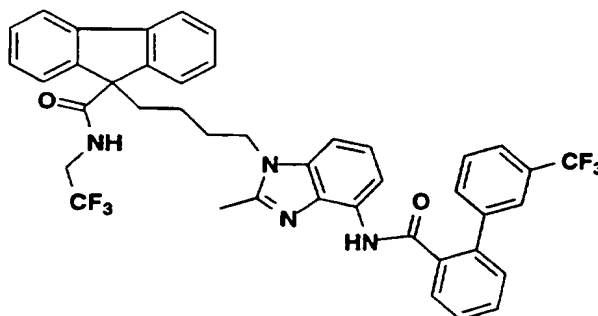


MS (M+H)⁺ = 798.

5

Example 588

9-[4-[2-Methyl-4-[[[3'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

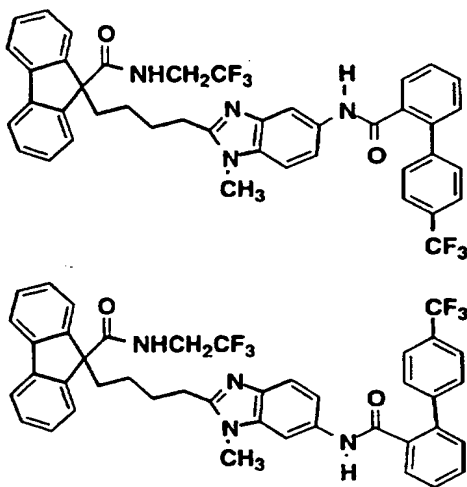


MS (ES, NH₃, + ions) m/z 741 (M+H).

10

Example 589

9-[4-[1-Methyl-5-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-2-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, and 9-[4-[1-methyl-6-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1H-benzimidazol-2-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide (1:1).

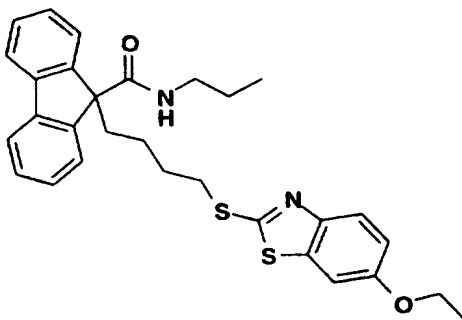


MS: $(M+H)^+ = 741$.

5

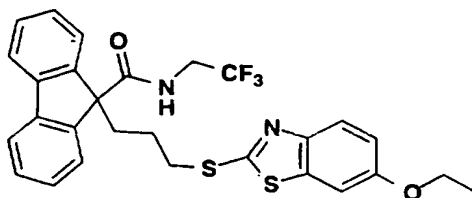
Example 590

9-[4-[(6-Ethoxy-2-benzothiazolyl)thio]butyl]-N-propyl-9H-fluorene-9-carboxamide.



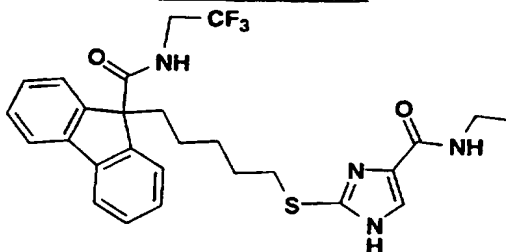
MS (ES) 517 $(M+H)^+$.

10

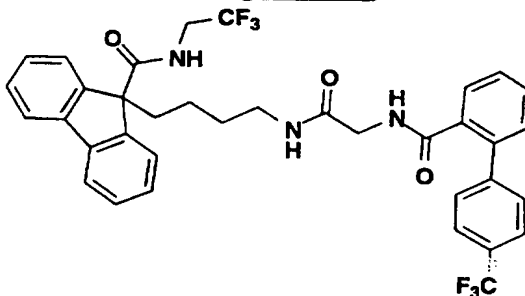
Example 591

MS (ESI, + ions): m/z 543 (M+H).

5

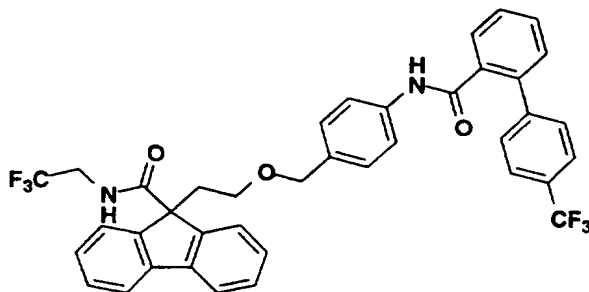
Example 592

MS (eletrospray, pos. ions): m/z 531 (M+H).

Example 593

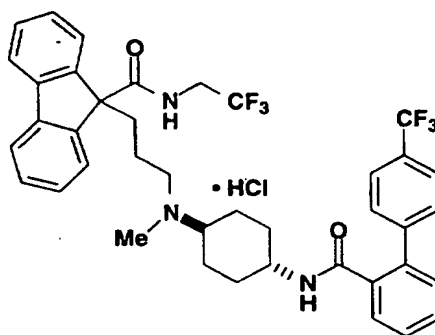
10

MS (eletrospray, pos. ions): m/z 668 (M+H).

Example 594

15 MS: (ESI, + ions) m/z 689 (M+H), 706 (M+NH₄).

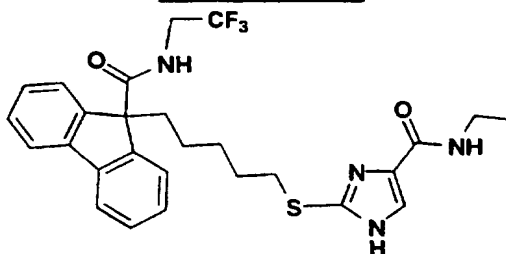
Example 595



MS (ES, + ions) m/z 708 [M+H].

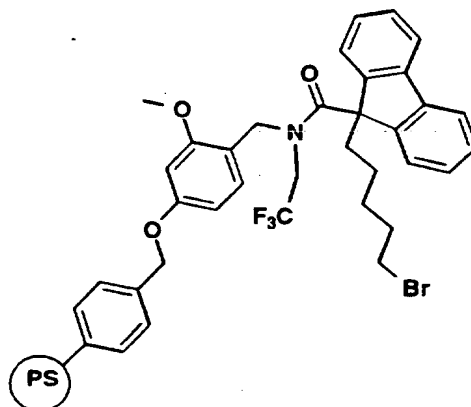
5

Example 596



The reaction sequence for preparation of title compound was carried out in batch mode until the final amide coupling which was carried out using a Varian Vac Elute SPS 24 as one of a 24 compound run. During the amide formation and cleavage all mixing was done by having the Vac Elute SPS 24 mounted to an orbital shaker. Mixing was done at 265 rpm unless otherwise noted.

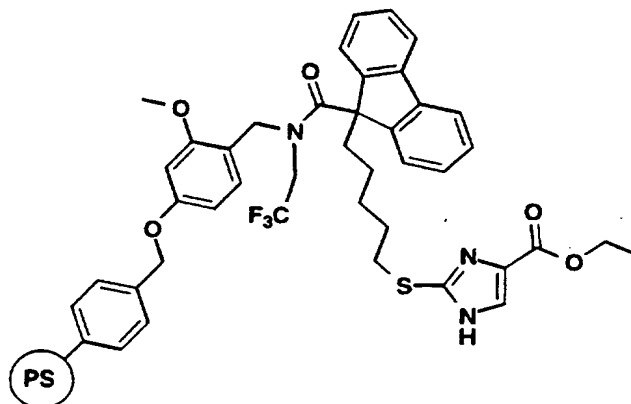
A.



PS = 1% Divinylbenzene cross-linked polystyrene resin, 100-200 mesh

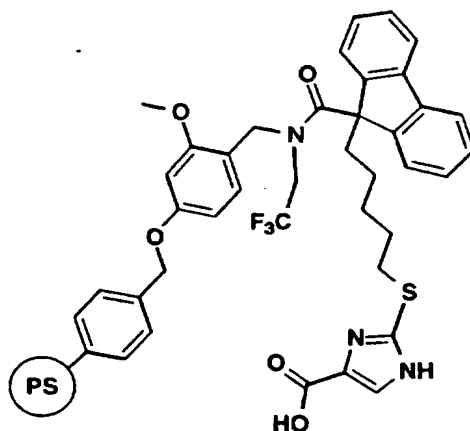
- 5 Title resin was prepared as described for Example 688 Part E except that 9-(5-bromopentyl)-9H-fluorene carboxylic acid chloride was used for the acylation with Example 689 Part A resin.

10 B.



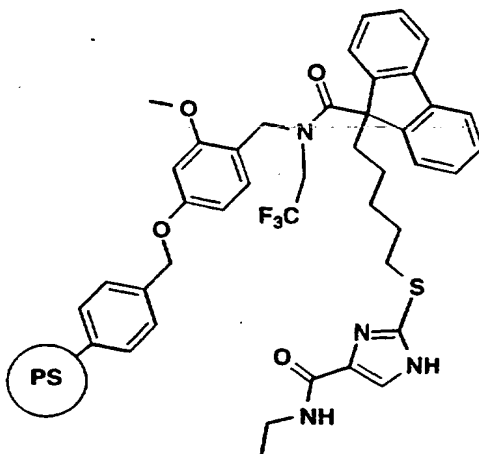
- 15 Title resin was prepared as described for Example 689 Part D compound employing 4-ethoxycarbonylimidazole-2-thiol (Maybridge Chemical Co.).

C.



Part B resin (6.6 mmol) was swollen in 40
5 mL of THF, followed by draining of the solvent
using nitrogen pressure. The resin was treated
with a solution of 5.6 g (99 mmol, 15 eq) of KOH in
15 mL of water, 30 mL of MeOH and 30 mL of THF.
The reaction mixture was heated at 50°C and
10 vortexed for 4 days. The reaction mixture was
cooled to RT and the reaction solution was removed.
The resin was rinsed with 1:1 THF:water (3 x 50
mL), THF (3 x 50 mL), 5% acetic acid in THF (3 x 30
mL), THF (3 x 50 mL), CH₂Cl₂ (3 x 50 mL) and MeOH
15 (3 x 50 mL). The title resin was used in the next
step without characterization.

D.



Method A.

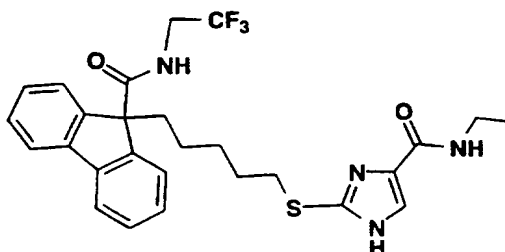
5 Part C resin (300 mg, 0.28 mmol) in a 25 mL polypropylene tube was swollen in 3 mL of CH_2Cl_2 and drained. The resin was suspended in 3 mL of a 1:1 CH_2Cl_2 :DMF solution and treated with 376 mg (1.9 mmol, 7 eq) of 1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride (EDC) and 267 mg (1.9 mmol, 7 eq) of 1-hydroxy-7-azabenzotriazole (HOAt). Diethylamine gas (was then bubbled into the reaction mixture for 5 min (≥ 10 eq)). The reaction mixture was shaken for 18 h, the reaction solution was drained and the resin was retreated under the same conditions. After 72 h, the reaction solution was again drained and the resin was rinsed with DMF (4 x 5 mL) and CH_2Cl_2 (4 x 5 mL). The title resin was used in the next step without characterization.

Method B

The Part C resin was swollen in 3 mL of CH_2Cl_2 and drained. The resin was suspended in 3 mL of a 1:1 CH_2Cl_2 :DMF solution and treated with 307 μL (247 mg, 1.9 mmol, 7 eq) diisopropylcarbodiimide and 342 mg (2.8 mmol, 10 eq) of 4-dimethylaminopyridine (DMAP). The

required amine (10 eq) was and the reaction mixture was shaken for 18 h. The reaction solution was drained and the resin was retreated under the same conditions. After 72 h, the reaction solution was again drained and the resin was rinsed with DMF (4 x 5 mL) and CH₂Cl₂ (4 x 5 mL). The resin was used in the next step without characterization.

E.



10

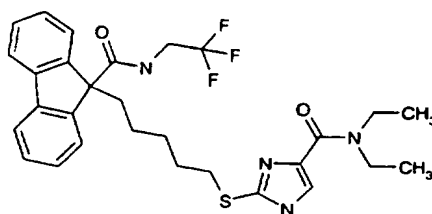
The Part D resin was treated with 2 mL of 100% trifluoroacetic acid and shaken for 90 min. The cleavage solution was collected, the resin was rinsed with CH₂Cl₂ (2 x 1 mL) and the combined cleavage solution and rinses were concentrated on a Speed Vac at RT. After 18 h, the sample was reconstituted in 4 mL of CH₂Cl₂ and reconstituted on the Speed Vac. After 18 h, the sample was again reconstituted in 4 mL of CH₂Cl₂ and aliquots were removed for HPLC and MS analysis. The tube was concentrated again on the Speed Vac at -40°C followed by exposure to high vacuum (1 mm Hg) on a lyophilizer for 14 h to afford 161 mg of crude product mixture of which 6 was 26%. The desired product was purified by preparative HPLC using a YMC-Pack ODS-A 250 x 30 mm, S-5 µm, 120 Å column with a 70-100 %B gradient over 30 min, holding at 100% B for 15 min at a flow of 25 mL/min (Solvent A: 90% H₂O/10% MeOH with 0.1% TFA; Solvent B: 90% MeOH/10% H₂O with 0.1% TFA) to provide 25 mg (17% based on starting aldehyde resin) of title compound as a cloudy oil.

HPLC: retention time: 4.7 min; 90% purity. HPLC conditions: YMC S3 ODS 4.6 x 50 mm

Rapid Resolution column; linear gradient from 50% B to 100% B over 8 min and held at 100% B for 2 min (method name: SMET4); flow rate 2.5 mL/min; detection at 215 nm; Solvent A: 90% H₂O/10% MeOH with 0.2% H₃PO₄; Solvent B: 90% MeOH/10% H₂O with 0.2% H₃PO₄.

10 MS(electrospray, pos. ions): m/z 531 (M + H)

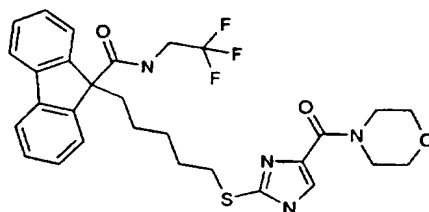
Example 597



MS: m/z 559 (M+H)

15

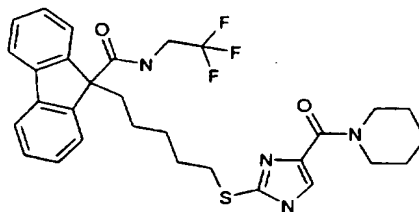
Example 598



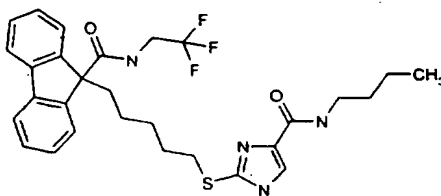
MS: m/z 573 (M+H)

20

Example 599

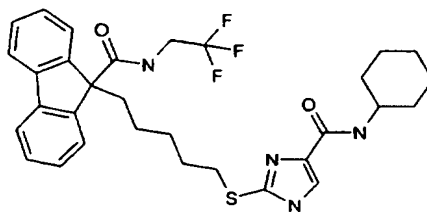


MS: m/z 571 (M+H)

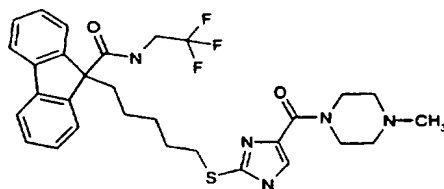
Example 600

MS: m/z 559 (M+H)

5

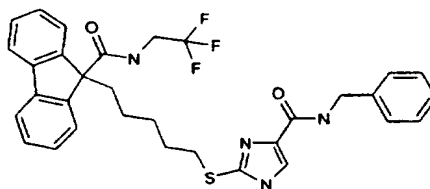
Example 601

MS: m/z 585 (M+H)

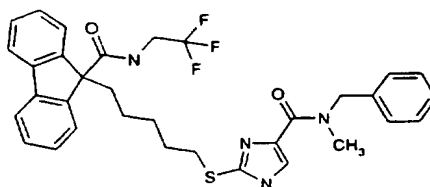
Example 602

10

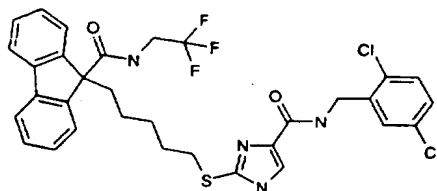
MS: m/z 586 (M+H)

Example 603

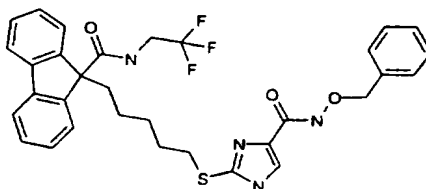
15 MS: m/z 593 (M+H)

Example 604

MS: m/z 607 (M+H)

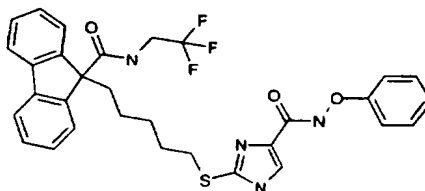
Example 605

5 MS: m/z 661 (M+H)

Example 606

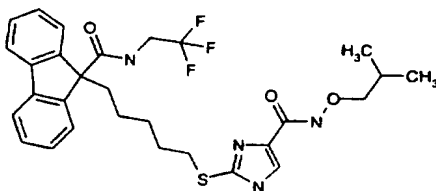
MS: m/z 609 (M+H)

10

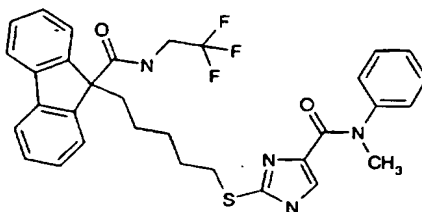
Example 607

MS: m/z 595 (M+H)

15

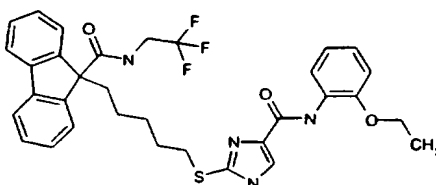
Example 608

MS: m/z 575 (M+H)

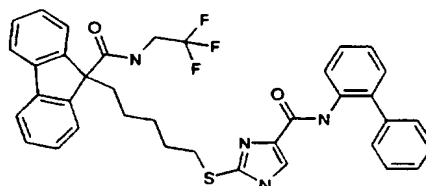
Example 609

MS: m/z 593 (M+H)

5

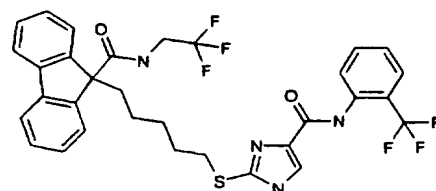
Example 610

MS: m/z 623 (M+H)

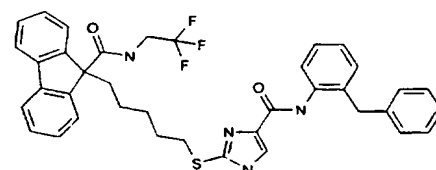
Example 611

10

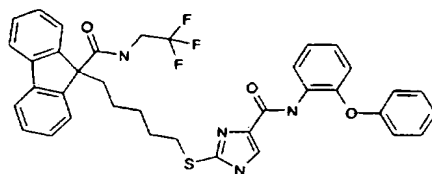
MS: m/z 655 (M+H)

Example 612

15 MS: m/z 647 (M+H)

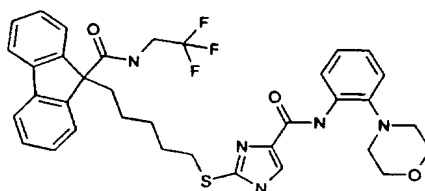
Example 613

MS: m/z 669 (M+H)

Example 614

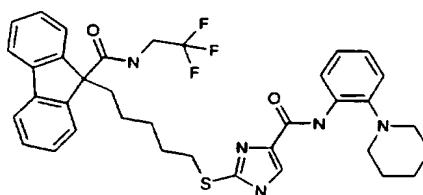
MS: m/z 671 (M+H)

5

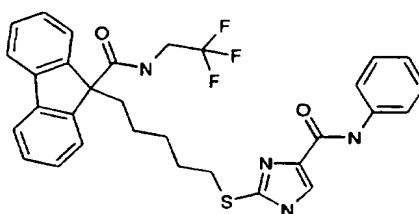
Example 615

MS: m/z 664 (M+H)

10

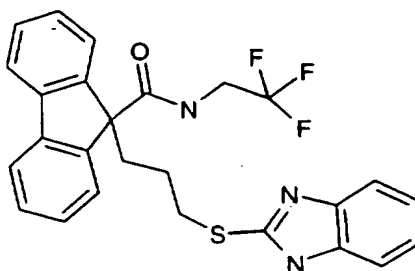
Example 616

MS: m/z 662 (M+H)

Example 617

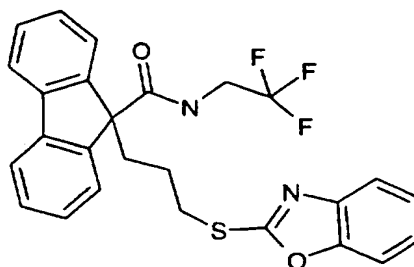
15

MS: m/z 579 (M+H)

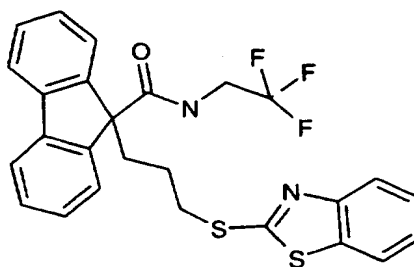
Example 618

MS: m/z 482 (M+H)

5

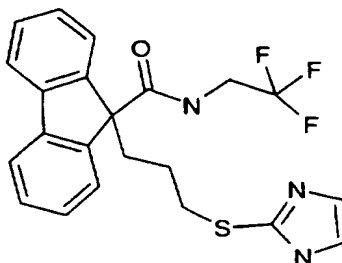
Example 619

MS: m/z 483 (M+H)

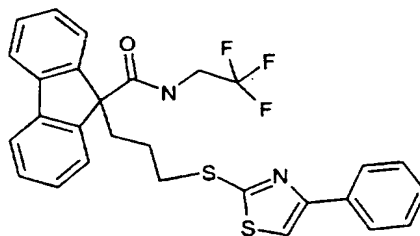
Example 620

10

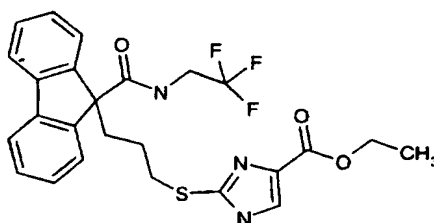
MS: m/z 499 (M+H)

Example 621

MS: m/z 432 (M+H)

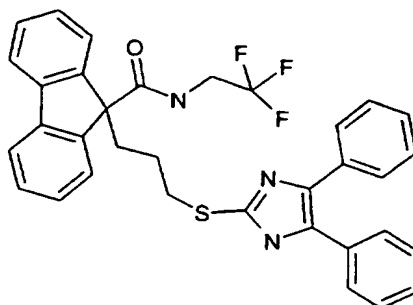
Example 622

5 MS: m/z 525 (M+H)

Example 623

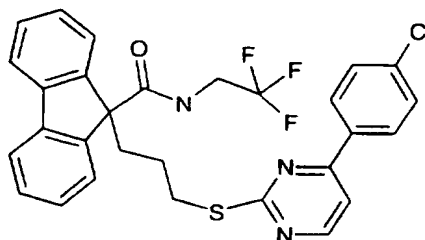
MS: m/z 504 (M+H)

10

Example 624

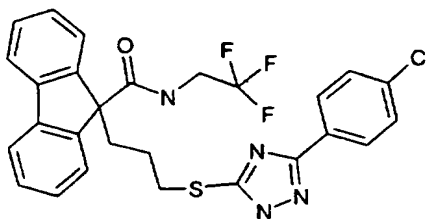
MS: m/z 584 (M+H)

15

Example 625

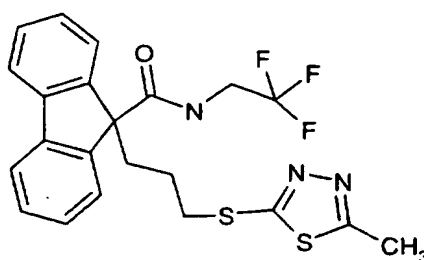
MS: m/z 554 (M+H)

Example 626



5 MS: m/z 543 (M+H)

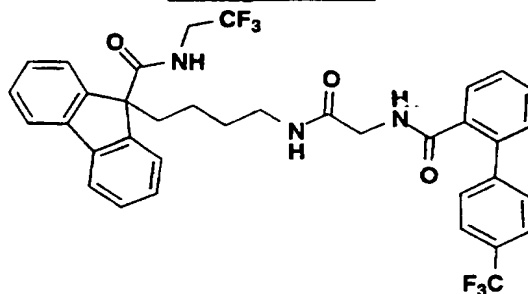
Example 627



MS: m/z 464 (M+H)

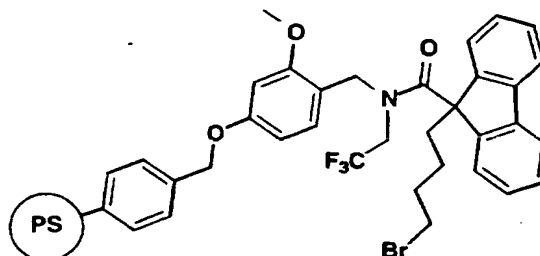
10

Example 628



15 The reaction sequence for preparation of title compound was carried out using the 48-Weller solid phase reactor mounted to an orbital shaker as part of a 48 compound run. Shaking was done at 300 rpm.

A.

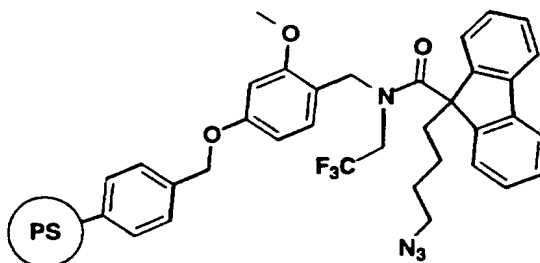


PS = 1% Divinylbenzene cross-linked polystyrene resin, 100-200 mesh

5 The title resin was prepared as described for Example 688 Part E except that 9-(4-bromobutyl)-9H-fluorene carboxylic acid chloride was used for the acylation with Example 689 Part A resin.

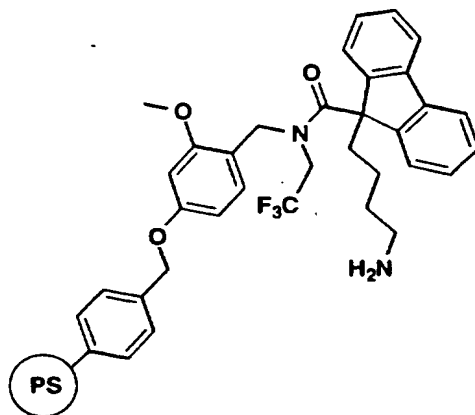
10

B.



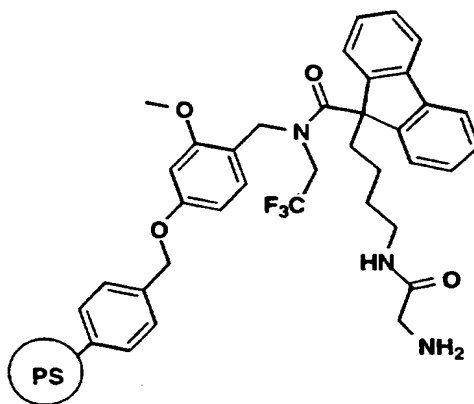
15 Part A resin (0.2 mmol) was swollen in 2 mL of dry DMF and drained using argon pressure. The resin was suspended in 1 mL of dry DMF and a solution of 284 mg (1 mmol, 5 eq) of tetrabutylammonium azide in 1 mL of DMF was added. After shaking for 16 h at RT, the reaction solution
20 was drained and the title resin was rinsed with DMF (2 x 2 mL) and THF (2 x 2 mL). The title resin was used in the next step without characterization.

C.



To the THF swollen Part B resin was added a
 5 solution of 262 mg (1 mmol, 5 eq) of triphenyl-
 phosphine and 1.26 mL (1.4 mmol, 7 eq) of water in
 2 mL of THF. After shaking for 7 h at RT, the
 reaction solution was drained and the resin was
 rinsed with THF (3 x 2 mL) and DMF (2 x 2 mL). The
 10 title resin was used in the next step without
 characterization.

D.

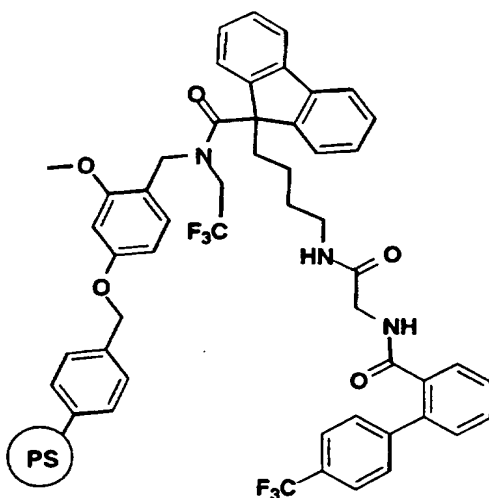


15

To the DMF swollen Part C resin were added
 a solution of 135 mg (1 mmol, 5 eq) of N-hydroxy-
 benzotriazole and 293 mg (1 mmol, 5 eq) of FMOC-
 glycine in 1.5 mL of DMF and a solution of 126 mg
 20 (1 mmol, 5 eq) of diisopropylcarbodiimide in
 CH₂Cl₂. After shaking for 12 h at RT, the reaction

solution was drained and the resin was retreated under the same conditions for 3 h. The reaction solution was drained and the resin was rinsed with DMF (1 x 2 mL), CH₂Cl₂ (2 x 2 mL) and DMF (2 x 2 mL). The resin was then treated with 3 mL of 30% piperidine in DMF. After shaking at RT for 30 min, the reaction solution was drained and the resin was treated again with 3 mL of 30% piperidine in DMF. After draining the reaction solution, the title resin was rinsed with DMF (3 x 2 mL). The title resin was used in the next step without characterization.

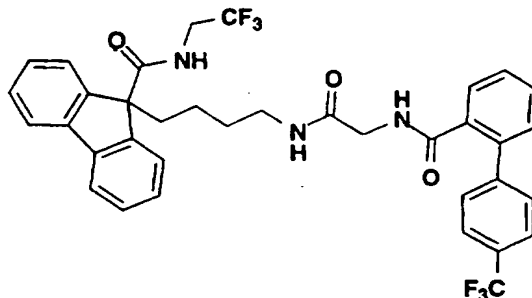
E.



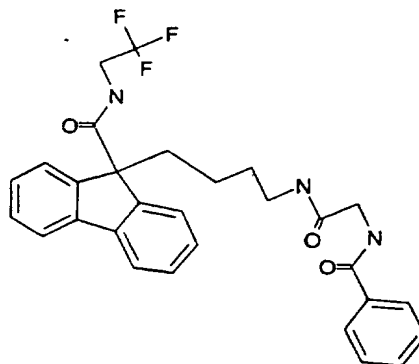
15

To the DMF swollen Part D resin were added solutions of 135 mg (1 mmol, 5 eq) of N-hydroxy-benzotriazole in 1 mL of DMF, 266 mg (1 mmol, 5 eq) of 4'-(trifluoromethyl)-2-biphenylcarboxylic acid in 1 mL of DMF and 126 mg (1 mmol, 5 eq) of diisopropylcarbodiimide in 0.5 mL of CH₂Cl₂. After shaking for 72 h at RT, the reaction solution was drained and the title resin was rinsed with DMF (1 x 2 mL) and CH₂Cl₂ (4 x 2 mL). The title resin was used in the next step without characterization.

F.

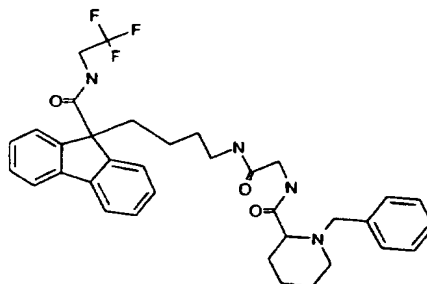


- The Part E resin was treated with 2 mL of
- 5 100% trifluoroacetic acid and shaken for 1 h. The cleavage solution was collected, the resin was rinsed with CH₂Cl₂ (2 x 1 mL) and the combined cleavage solution and rinses were concentrated on a Speed Vac at RT. After 18 h, the sample was
- 10 reconstituted in 4 mL of CH₂Cl₂ and reconstituted on the Speed Vac. After 18 h, the sample was again reconstituted in 4 mL of CH₂Cl₂ and aliquots were removed for HPLC and MS analysis. The tube was concentrated again on the Speed Vac followed by
- 15 exposure to high vacuum (1 mm Hg) on a lyophilizer for 14 h to afford 110 mg (82% yield based on starting aldehyde resin) of title compound as clear yellow oil.
- 20 HPLC: retention time: 7.7 min; 86% purity. HPLC conditions: YMC S3 ODS 4.6 x 50 mm Rapid Resolution column; linear gradient from 20% B to 100% B over 8 min and held at 100% B for 2 min (method name: SMET2); flow rate 2.5 mL/min;
- 25 detection at 215 nm; Solvent A: 90% H₂O/10% MeOH with 0.2% H₃PO₄; Solvent B: 90% MeOH/10% H₂O with 0.2% H₃PO₄.
- MS (electrospray, pos. ions): m/z 668 (M + H)

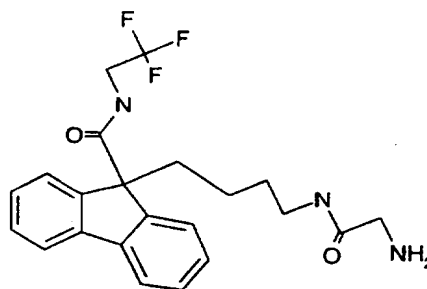
Example 629

MS: m/z 524 (M+H)

5

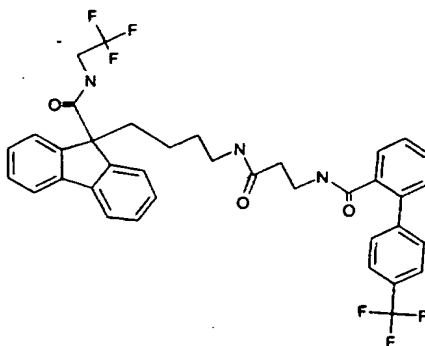
Example 630

MS: m/z 621 (M+H)

Example 631

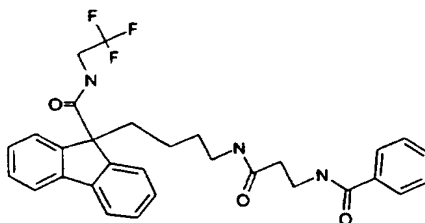
10

MS: m/z 420 (M+H)

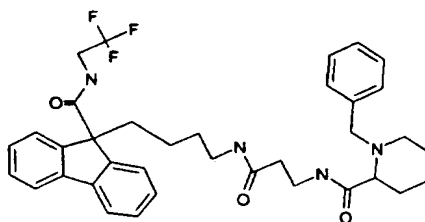
Example 632

MS: m/z 682 (M+H)

5

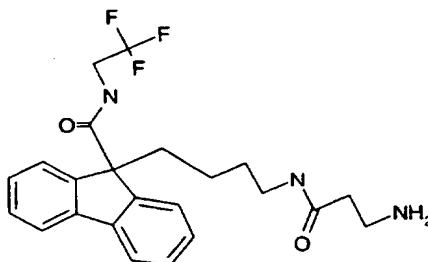
Example 633

MS: m/z 538 (M+H)

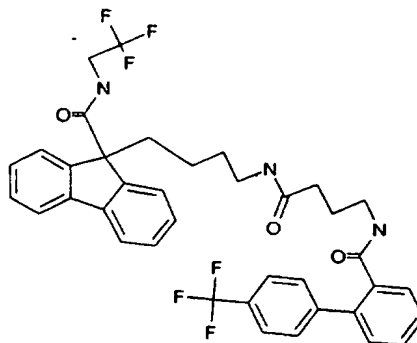
Example 634

10

MS: m/z 635 (M+H)

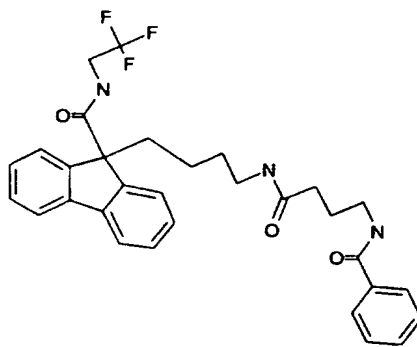
Example 635

15 MS: m/z 434 (M+H)

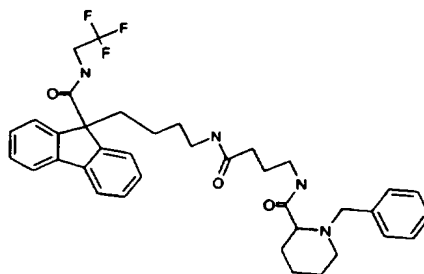
Example 636

MS: m/z 696 (M+H)

5

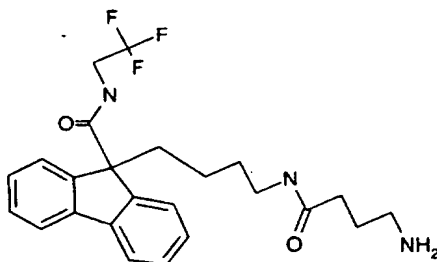
Example 637

MS: m/z 552 (M+H)

Example 638

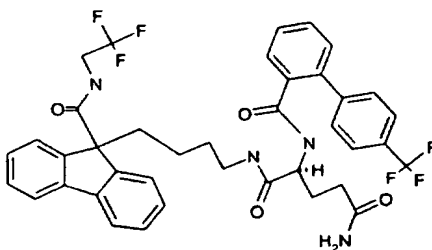
10

MS: m/z 649 (M+H)

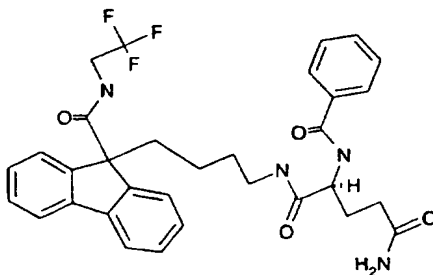
Example 639

MS: m/z 448 (M+H)

5

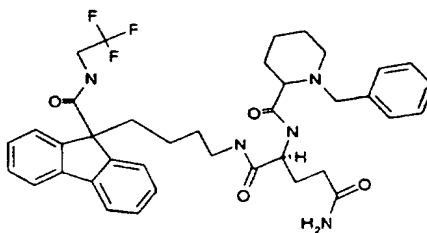
Example 640

MS: m/z 739 (M+H)

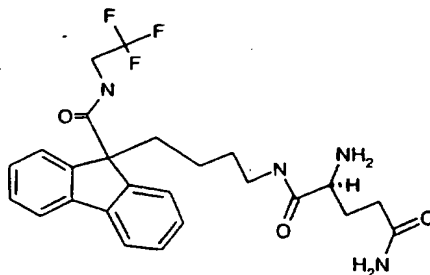
Example 641

10

MS: m/z 595 (M+H)

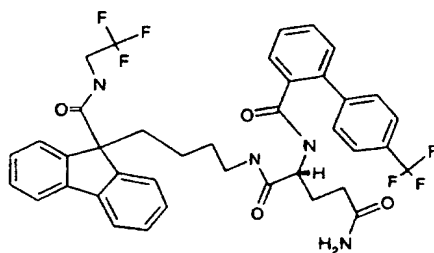
Example 642

15 MS: m/z 692 (M+H)

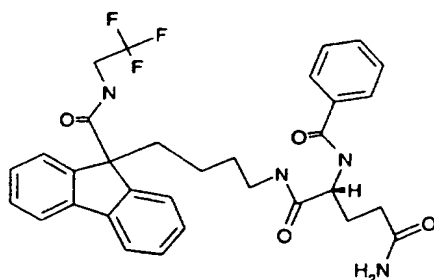
Example 643

MS: m/z 491 (M+H)

5

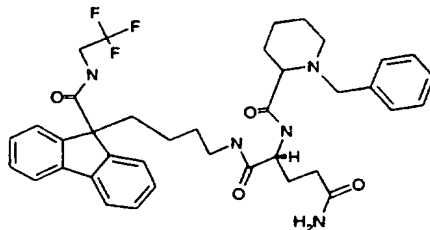
Example 644

MS: m/z 739 (M+H)

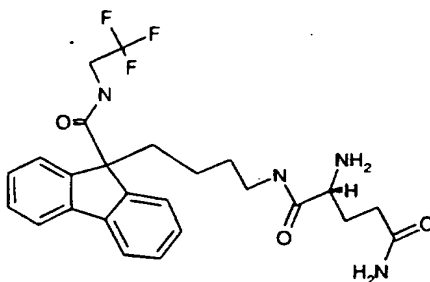
Example 645

10

MS: m/z 595 (M+H)

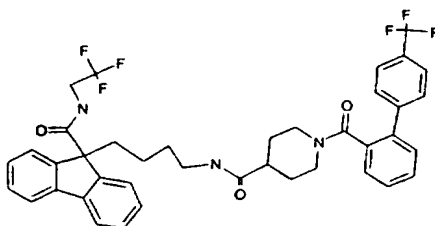
Example 646

15 MS: m/z 692 (M+H)

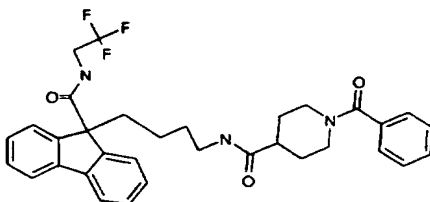
Example 647

MS: m/z 491 (M+H)

5

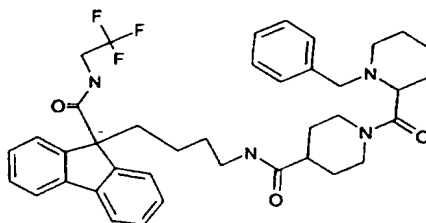
Example 648

MS: m/z 722 (M+H)

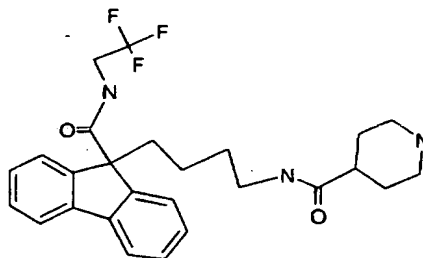
Example 649

10

MS: m/z 578 (M+H)

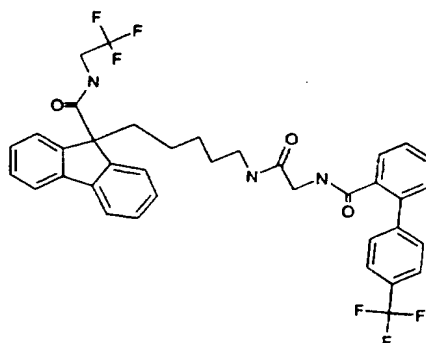
Example 650

15 MS: m/z 675 (M+H)

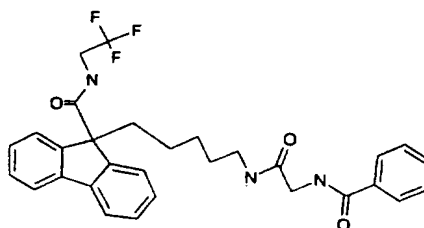
Example 651

MS: m/z 474 (M+H)

5

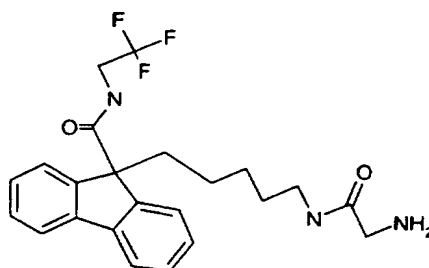
Example 652

MS: m/z 682 (M+H)

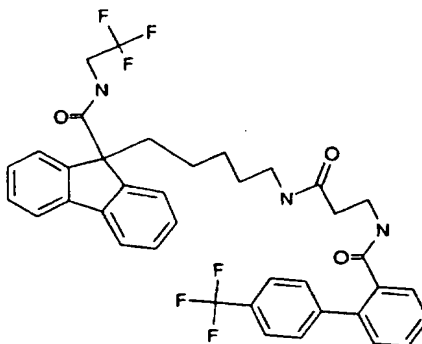
Example 653

10

MS: m/z 538 (M+H)

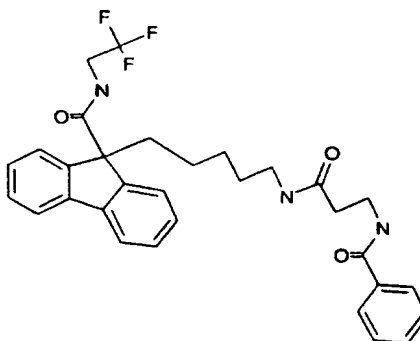
Example 654

15 MS: m/z 434 (M+H)

Example 655

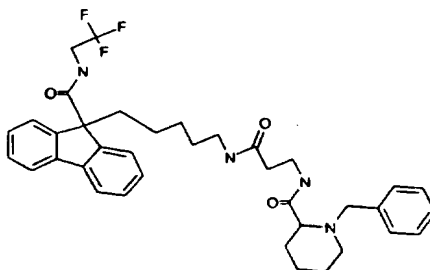
MS: m/z 696 (M+H)

5

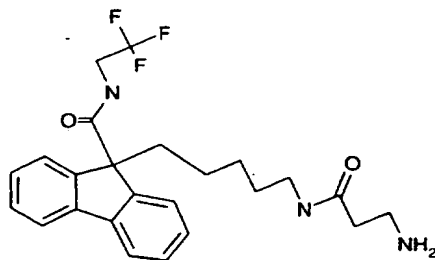
Example 656

MS: m/z 552 (M+H)

10

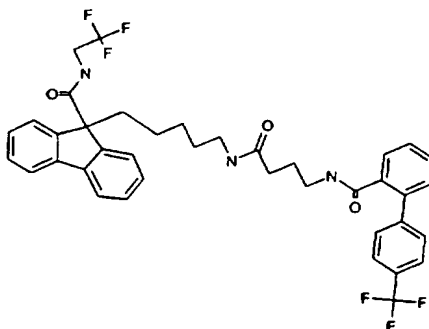
Example 657

MS: m/z 649 (M+H)

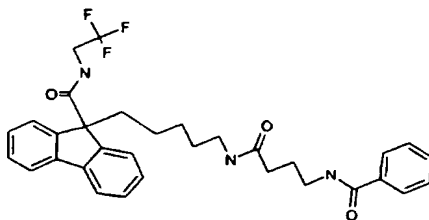
Example 658

MS: m/z 448 (M+H)

5

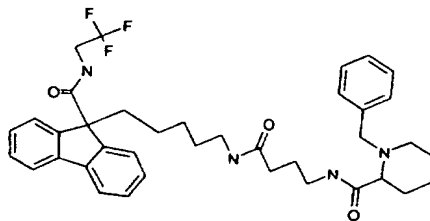
Example 659

MS: m/z 710 (M+H)

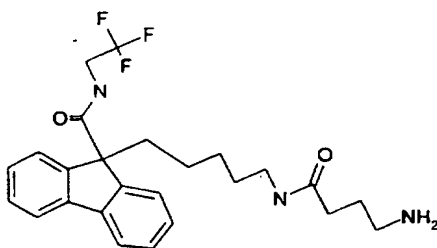
Example 660

10

MS: m/z 566 (M+H)

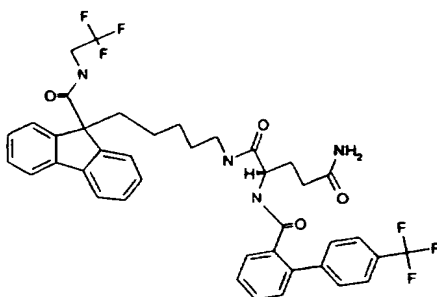
Example 661

15 MS: m/z 663 (M+H)

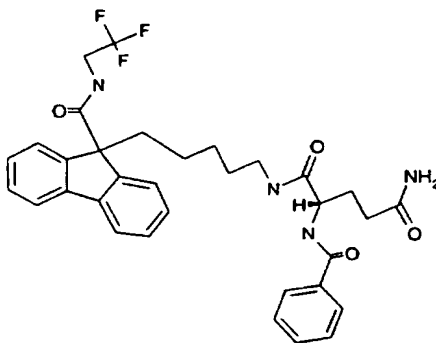
Example 662

MS: m/z 462 (M+H)

5

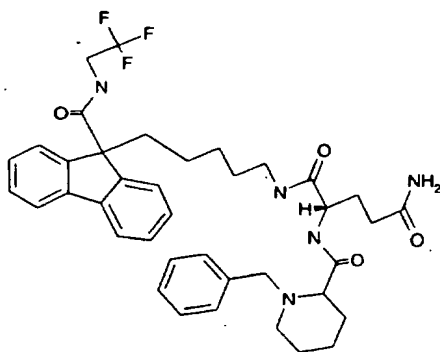
Example 663

MS: m/z 753 (M+H)

Example 664

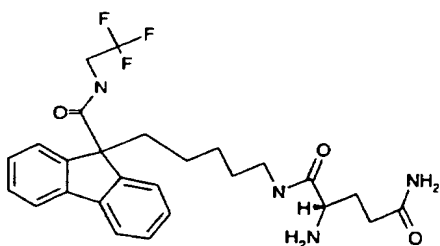
10

MS: m/z 609 (M+H)

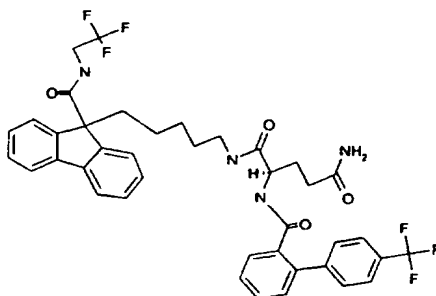
Example 665

MS: m/z 706 (M+H)

5

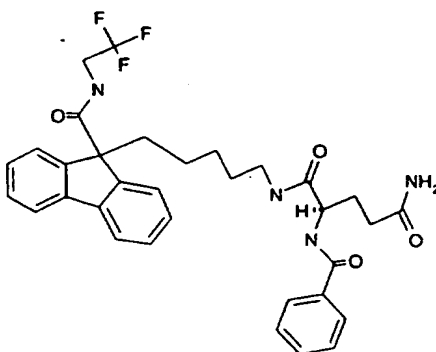
Example 666

MS: m/z 505 (M+H)

Example 667

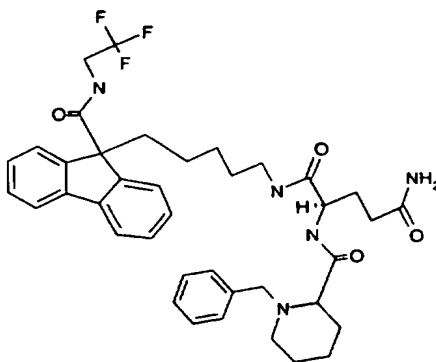
10

MS: m/z 753 (M+H)

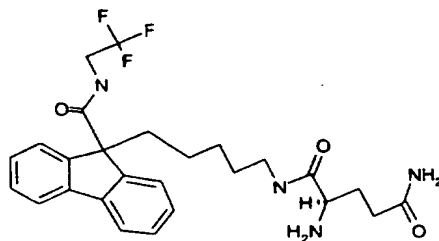
Example 668

MS: m/z 609 (M+H)

5

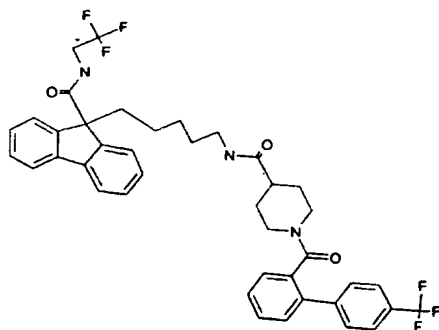
Example 669

MS: m/z 706 (M+H)

Example 670

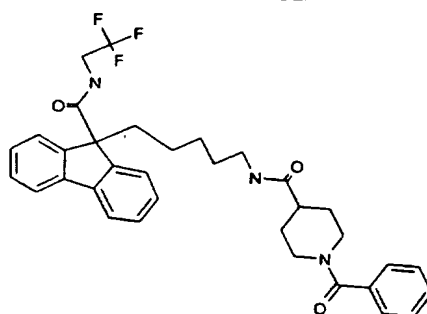
10

MS: m/z 505 (M+H)

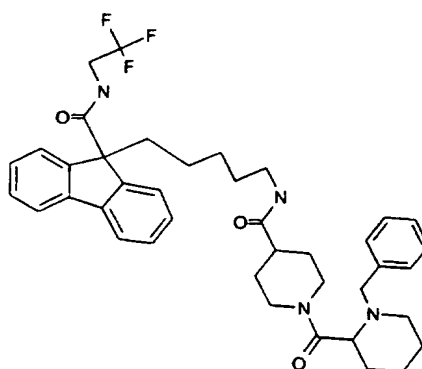
Example 671

MS: MS: m/z 736 (M+H)

5

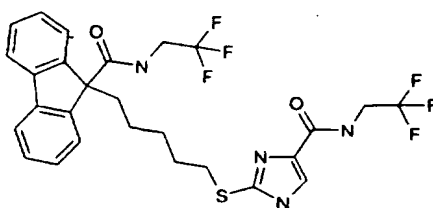
Example 672

MS: m/z 592 (M+H)

Example 673

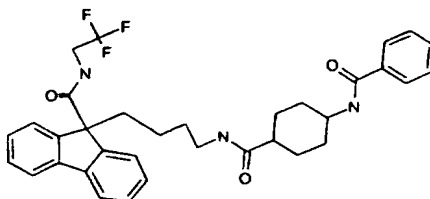
10

MS: m/z 689 (M+H)

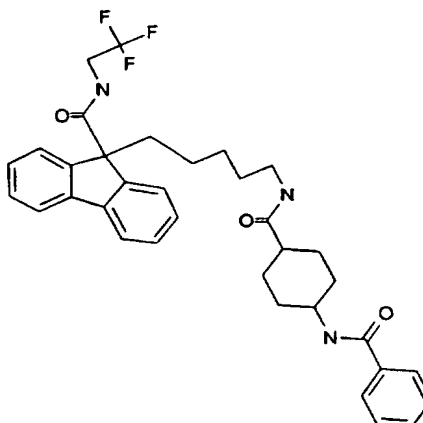
Example 674

MS: m/z 585 (M+H)

5

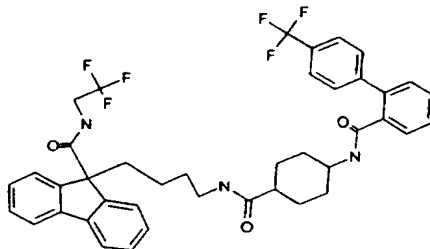
Example 675

MS: m/z 592 (M+H)

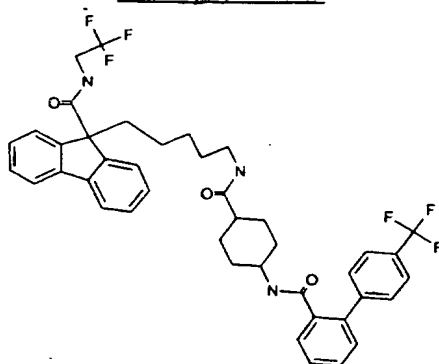
Example 676

10

MS: m/z 606 (M+H)

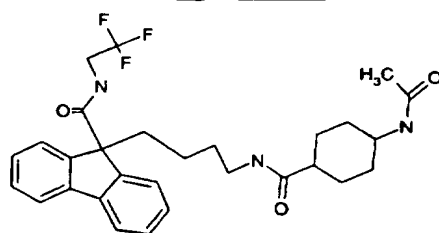
Example 677

15 MS: m/z 736 (M+H)

Example 678

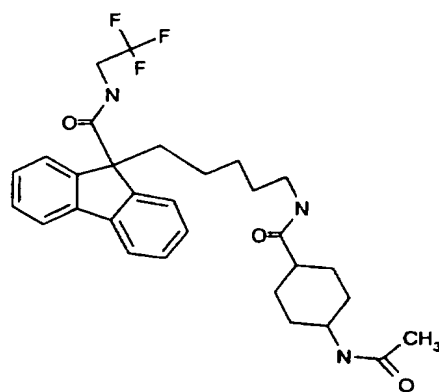
MS: m/z 750 (M+H)

5

Example 679

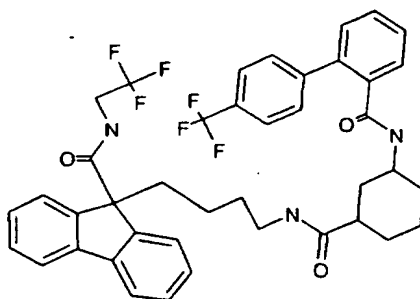
MS: m/z 530 (M+H)

10

Example 680

MS: m/z 544 (M+H)

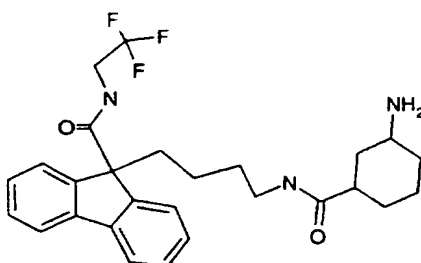
Example 681



MS: m/z 736 (M+H)

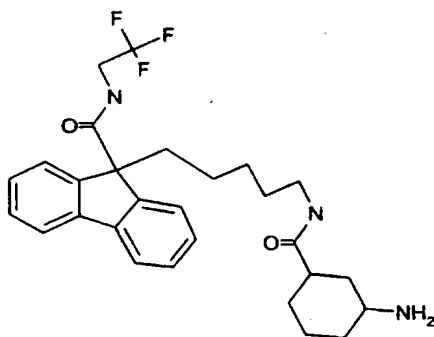
5

Example 682



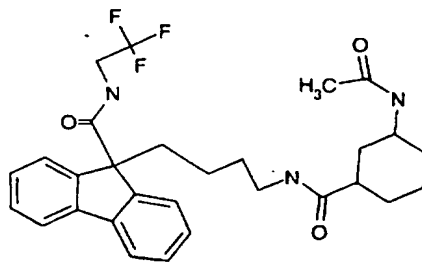
MS: m/z 488 (M+H)

Example 683



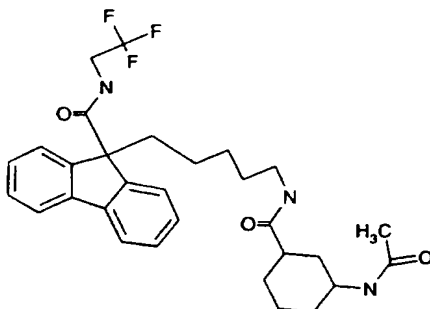
10

MS: m/z 502 (M+H)

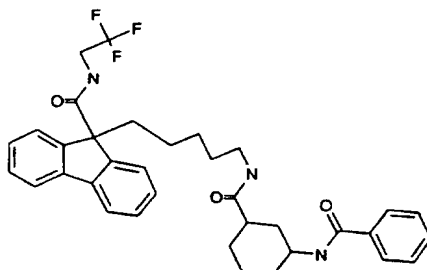
Example 684

MS: m/z 530 (M+H)

5

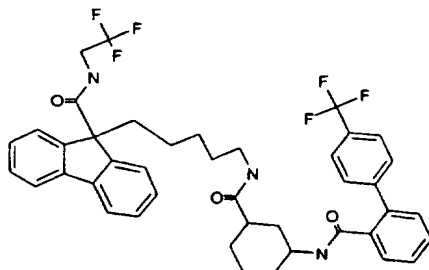
Example 685

MS: m/z 544 (M+H)

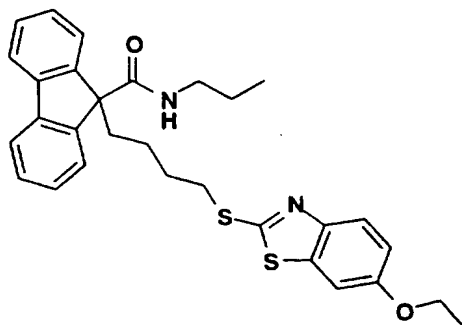
Example 686

10

MS: m/z 606 (M+H)

Example 687

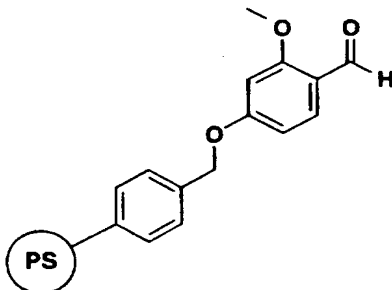
MS: m/z 750 (M+H)

Example 688

9-[4-[(6-Ethoxy-2-benzothiazolyl)thio]butyl]-N-propyl-9H-fluorene-9-carboxamide.

5

A.



PS = 1% Divinylbenzene cross-linked polystyrene resin, 100-200 mesh

- 10 To a magnetically stirred suspension of 4.8
g (120 mmol, 10 eq) of sodium hydride (60% mineral
oil dispersion) in 30 mL of dimethylformamide (DMF)
at 0 °C was added a solution of 18.2 g (120 mmol,
10 eq) of 4-hydroxy-2-methoxybenzaldehyde in 50 mL
15 of DMF dropwise over 75 min. The reaction was
allowed to warm to room temperature (RT) and
stirred for an additional 75 min. The stirbar was
removed and 10 g (12 mmol, 1 eq) of Merrifield
resin (with a loading of 1.2 mmol/g (Advanced
20 Chemtech)) was added. The flask was placed in a
heating mantel mounted on a vortex mixer and heated
at 70°C (internal temper-ature) while vortexing for
26 h. The contents of the reaction vessel were
transferred to a large filter funnel with a
25 scintered-glass frit (porosity C) and rinsed

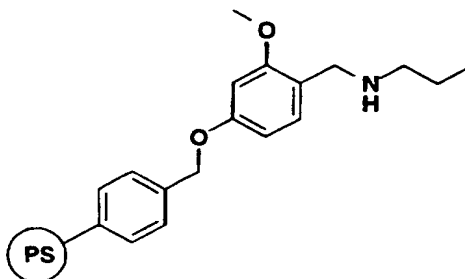
sequentially with DMF (3 x 100 mL), 1:1 DMF:water (3 x 100 mL), water (2 x 100 mL) and MeOH (5 x 100 mL). The resin was dried under high vacuum (0.1 mm Hg) for 72 h to afford 11.16 g (98% of expected weight) of title compound as a tacky non-freeflowing tan resin. The resin was characterized by gel-phase ^{13}C -NMR and elemental analysis (chlorine and oxygen).

10 Elemental Analysis:

Chlorine: Expected 0% Cl for 100% loading; found 0.21%. Starting Cl content of resin was 4.26%. Residual Cl consistent with 95% resin loading.

15 Oxygen: Expected 5.76% for 100% loading; found 6.21%.

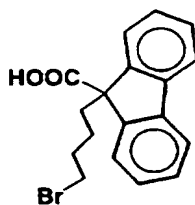
B.



20 To a 25 mL Varian polypropylene tube fitted with a polyethylene frit and a luer stopcock was added 500 mg of Part A resin. The tube was sealed with a 19 mm Aldrich Suba septa and the resin was swollen in 5 mL of dry DMF, mixed by vortexing for
25 1 min and the DMF was removed using vacuum and N_2 pressure in order to maintain the vessel under inert atmosphere. Trimethyl orthoformate (1 mL) was added followed by 3.2 mL of DMF and 0.8 mL (10.0 mmol, 18 eq) of n-propylamine. The reaction
30 mixture was vortexed for 18 h at RT. After removal of the reaction solution by nitrogen pressure and vacuum, 5 mL of a 200 mg/mL solution of sodium

triacetoxy-borohydride in DMF (1 g, 4.7 mmol, 8 eq) and 100 μ L of acetic acid were added. The reaction mixture was vortexed for 8 h at RT. The reaction solution was removed and the so-formed title resin
5 was rinsed with DMF (4 x 5 mL), 1:1 DMF:water (2 x 5 mL), water (1 x 5 mL), DMF (3 x 5 mL) and dichloromethane (CH_2Cl_2) (4 x 5 mL). The last CH_2Cl_2 rinse was done with dry CH_2Cl_2 in the tube with the septa in place using nitrogen gas and
10 vacuum to filter away the solvent and keep the reaction vessel under inert atmosphere. The title resin was used in the next step without characterization.

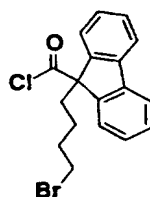
15 C.



The title compound was prepared as described in Example 273 Part A(1).

20

D.

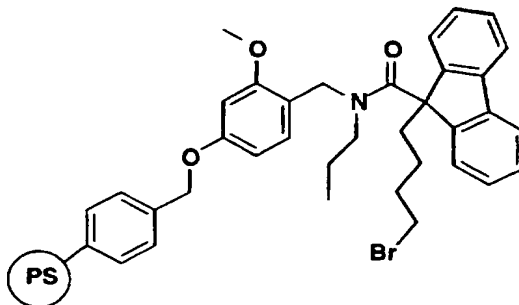


To 3.45 g (10 mmol, 1 eq) of 9-(4-bromobutyl)-9H-fluorene carboxylic acid (Part C) in
25 15 mL of CH_2Cl_2 was added 100 μ L of DMF. The resulting solution was cooled to 0°C and 7.5 mL (15 mmol, 1.5 eq) of a 2.0 M oxalyl chloride solution in CH_2Cl_2 was added. The bubbling reaction mixture
30 was stirred at 0°C for 15 min and then allowed to warm to RT. After 2 h, the reaction mixture was

concentrated to afford the title crude acid chloride as a yellowish orange solid/oil mixture which was dissolved in CH_2Cl_2 and used without purification.

5

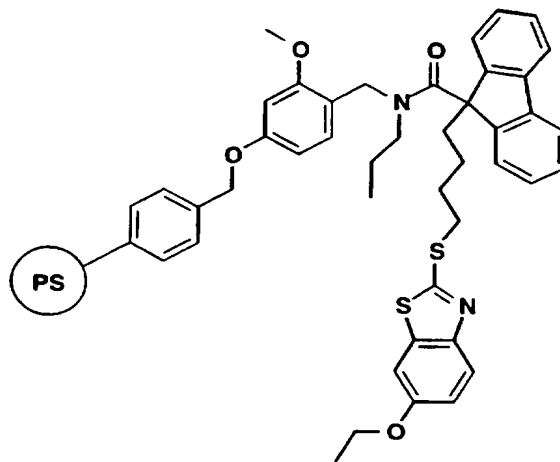
E.



To the Part B resin in the polypropylene
10 tube were added 1 mL of diisopropylethyl amine (5.7 mmol, 10 eq) and 1 mL of CH_2Cl_2 and the resulting mixture was mixed for 2 min. The tube was cooled to 0°C in an ice bath and 4 mL (2.2 mmol, 4 eq) of a solution of Part D acid chloride in CH_2Cl_2 was
15 added. The resulting orange reaction mixture was mixed by vortexing at RT for 19 h. and then rinsed with CH_2Cl_2 (4 x 5 mL) to afford title resin which was in the next step without characterization.

20

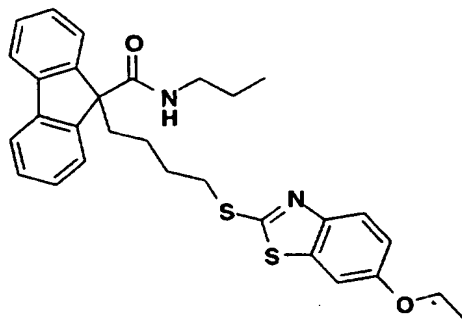
F.



The Part E resin in the sealed polypropylene tube was swollen in 5 mL of dry DMF and vortexed for 2 min. The solvent was removed with N₂ and vacuum and a solution of 1.16 g (5.5 mmol, 10 eq) of 6-ethoxy-2-mercaptobenzothiazole (Aldrich) in 4 mL of DMF was added to the resin followed by 5 mL (5 mmol, 9 eq) of a 1.0 M solution of sodium bistrimethyl-silylamide in THF. Vortexing was initiated and the reaction mixture was mixed for 17 h at RT. The reaction solution was filtered away and the title resin was rinsed with DMF (4 x 5 mL), 1:1 DMF:water (2 x 5 mL), water (1 x 5 mL), DMF (3 x 5 mL) and dichloromethane (CH₂Cl₂) (4 x 5 mL).

15

G.



The Part F resin was treated with 5 mL of 100% trifluoroacetic acid and vortexed for 90 min. The reaction solution was collected, the resin was rinsed with CH₂Cl₂ (3 x 1 mL) and the combined reaction solution and rinses were concentrated. The products from 3 parallel reactions were each redissolved in 15 mL of CH₂Cl₂, pooled and reconcentrated to afford 393 mg (46% crude) of an off-white solid. Recrystallization from MeOH afforded 339 mg (40%) of title compound as a white solid.

30

m.p. 112-113.5°C

TLC (silica gel, 5% MeOH in CH₂Cl₂, UV and I₂)

R_f = 0.75;

IR(KBr): 3343, 2924, 1653, 1522, 1449, 1225,
739 cm⁻¹;

5 MS(electrospray, pos. ions): m/z 517 (M + H);

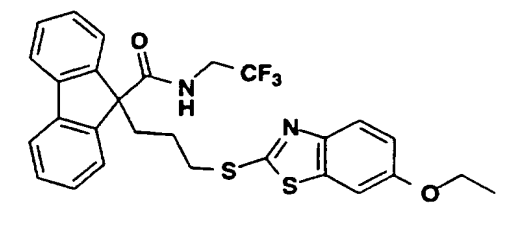
Anal. Calcd for C₃₀H₃₂N₂O₂S₂:

C, 69.73; H, 6.24; N, 5.42; S, 12.41

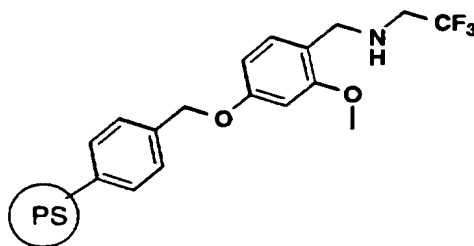
Found: C, 69.48; H, 6.22; N, 5.39; S, 12.25.

10

Example 689



A.

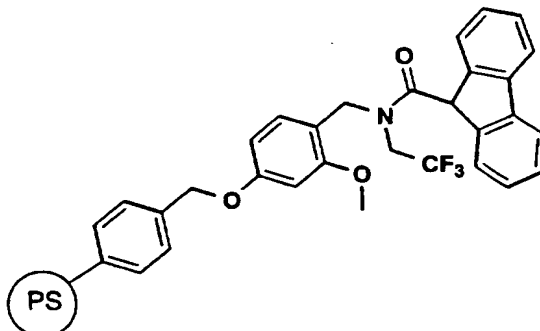


15

Example 688 Part A resin (250 mg, 0.3 mmol) was swollen in 3.0 mL of dimethylformamide (DMF). The solvent was drained. and 406 mg (3.0 mmol, 10 eq) of trifluoroethylamine, 261 μ L (1.5 mmol, 5 eq) of diisopropylethylamine, 0.5 mL of trimethylorthoformate and 1.8 mL of DMF were added. The reaction mixture was shaken on a vortex mixer for 3.5 hours. The reaction solution was drained and 2.5 mL of a 200 mg/mL solution of sodium triacetoxyborohydride (500 mg) and 100 μ L of acetic acid were added. The mixture was shaken for 16 hours. The resin was rinsed with 3 x 3 mL of the following: DMF, 1:1 DMF:H₂O, H₂O, DMF, followed by 5 x 3 mL each of CH₂Cl₂ and CH₃OH. The resin was dried under vacuum

to provide 262 mg of title compound as a white resin.

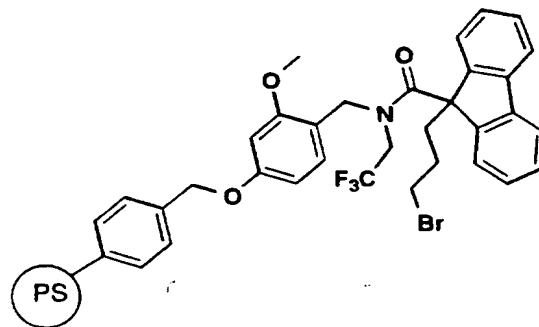
B.



5

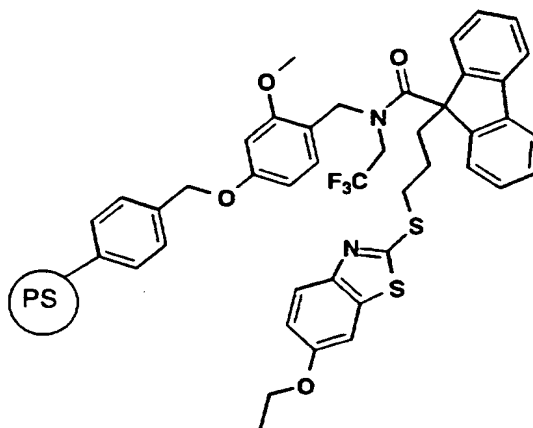
The Part A resin (262 mg, 0.3 mmol) was swollen in 3.0 mL of methylene chloride. A solution of 204 mg of 1-hydroxy-7-azabenzotriazole (1.5 mmol, 5 eq) and 315 mg of 9-fluorenenecarboxylic acid (1.5 mmol, 5 eq) in 1.0 mL of DMF and 2.0 mL of methylene chloride was treated with 235 μ L of diisopropyl-carbodiimide (1.5 mmol, 5 eq). The resin was drained, the reagent solution was added and the mixture was shaken for 17 hours. The reaction solution was drained and rinsed with 3 x 3 mL of the following: DMF, 1:1 DMF:H₂O, H₂O, DMF, followed by 5 x 3 mL each of CH₂Cl₂ and CH₃OH. The resin was dried under vacuum to provide 356 mg of title compound as a yellow resin.

C.



The Part B resin (323 mg, 0.27 mmol) was swollen in 3.0 mL of DMF (new Sure-Seal) and then drained under an atmosphere of argon. DMF (2.5 mL) was added, followed by the dropwise addition of 324 μ L (3.2 mmol, 1.2 eq) of a 1.0 M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (THF). The reaction mixture was shaken under argon for two hours. The reaction solution was drained and the resin was rinsed with 6 x 3 mL of DMF maintaining an argon atmosphere. The resin was suspended in 2.5 mL of DMF and 137 μ L of 1,3 dibromopropane (1.35 mmol, 5 eq) was added. The mixture was shaken for 4 hours. The reaction solution was drained and the resin was rinsed with 3 x 3 mL of the following: DMF, 1:1 DMF:H₂O, H₂O, followed by 4 x 3 mL of DMF to provide title resin, used as is in the next step.

D.



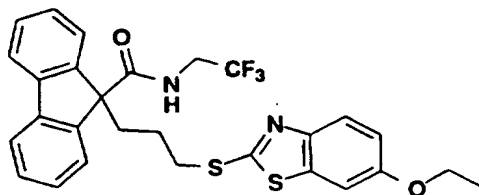
20

The Part C resin (0.27 mmol) was swollen in 3.0 mL of DMF. The solvent was drained and a solution of 570 mg of 6-ethoxy-2-mercaptobenzo-thiazole (2.7 mmol, 10 eq) in 3.0 mL of DMF was added, followed by the dropwise addition of 2.7 mL (2.7 mmol, 10 eq) of a 1.0 M solution of sodium bis(trimethylsilyl)amide in THF. After the addition was completed, the mixture was shaken for

14 hours. The resin was rinsed with 3 x 3 mL of the following: DMF, 1:1 DMF:H₂O, H₂O, DMF, followed by 8 x 3 mL of CH₂Cl₂ to provide title resin, used as is in the next step.

5

E.



The Part D resin (0.27 mmol) was treated
10 with 3.0 mL of trifluoroacetic acid for 90 minutes
and then rinsed with methylene chloride, and the
solutions were concentrated to provide 86 mg (58%)
of a brown solid. This solid was combined with
another batch of product prepared by the same route
15 and purified by flash chromatography on silica gel
(50 g) packed, loaded, and eluted with 25% hexane
in methylene chloride followed by 100% methylene
chloride. The 100% methylene chloride fractions
were concentrated to provide 198 mg of title
20 compound as an off-white foam.

TLC Silica gel (9:1 methylene chloride/hexane,
visualization by UV) R_f = 0.25.

HPLC Purity = 97%. Retention time = 9.0 min.

25 Column: Zorbax SB- C18 Rapid Resolution 4.6 x 75
mm. Solvent A: 10% methanol:90% water:0.2% H₃PO₄.

Solvent B: 90% methanol:10% water:0.2% H₃PO₄.

Elution: Linear gradient from 20 to 100% B over 8
minutes followed by isocratic 100% B for 2 minutes

30 (Short Method 2-SMET2).

MS (ESI, + ions): m/z 543 (M + H).

IR (KBr) 2930, 1684, 1601, 1512, 1449, 1273, 1223,
1163, 1038, 997, 745 cm⁻¹.

Anal. Calcd for $C_{28}H_{25}N_2O_2S_2F_3$:

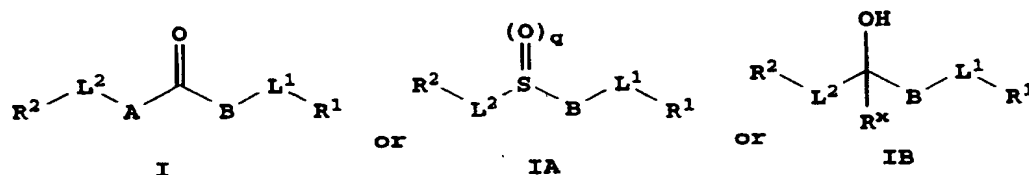
C, 61.98; H, 4.64; N, 5.16; S, 11.82;
F, 10.50

Found: C, 61.90; H, 4.72; N, 5.06; S, 12.09;

5 F, 10.23.

What is Claimed is:

1. A compound which has the structure



5 including pharmaceutically acceptable salts thereof, N-oxides thereof,

wherein q is 0, 1 or 2;

A is (1) a bond;

(2) -O-; or

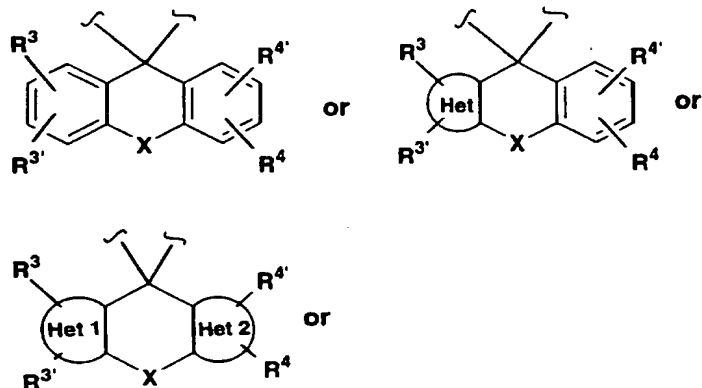
10

(3) $\begin{array}{c} \text{---N---} \\ | \\ \text{R}^5 \end{array}$

where R⁵ is H or lower alkyl, or R⁵ together with R² forms a carbocyclic or heterocyclic ring system containing 4 to 8 members in the ring;

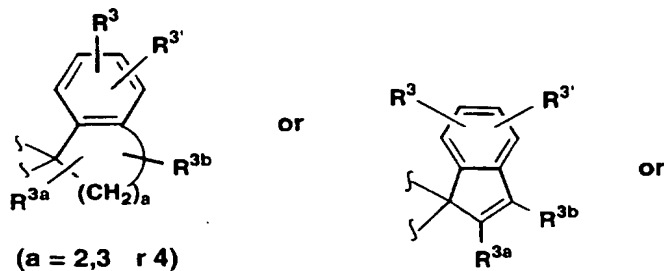
B is a fluorenyl-type group of the

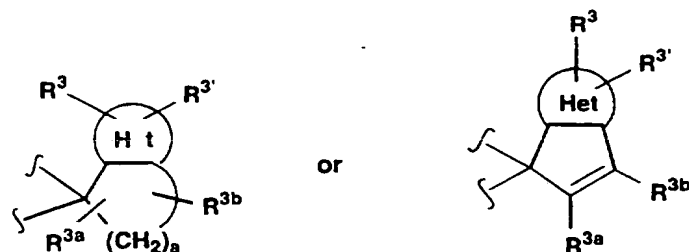
15 structure



20

B is an indenyl-type group of the structure

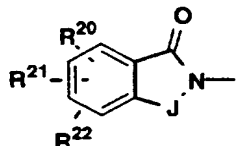




R^x is H, alkyl or aryl;

- 5 R^1 is H, alkyl, alkenyl, alkynyl, alkoxy, (alkyl or aryl)₃Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, substituted alkylamino, substituted arylalkylamino, aryl, arylalkyl, arylamino, aryloxy, heteroaryl, heteroaryl amino, heteroaryloxy, arylsulfonylamino, heteroarylsulfonylamino, arylthio, arylsulfinyl, arylsulfonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, cycloheteroalkyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl,
- 10 -PO(R^{13})(R^{14}), (where R^{13} and R^{14} are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy);
- 15 aminocarbonyl (where the amino may optionally be substituted with one or two aryl, alkyl or heteroaryl groups); cyano, 1,1-(alkoxy or aryloxy)₂alkyl (where the two aryl or alkyl substituents can be independently defined, or
- 20 linked to one another to form a ring connected to L^1 (or L^2 in the case of R^2) at the 2-position); 1,3-dioxane or 1,3-dioxolane connected to L^1 (or L^2 in the case of R^2) at the 4-position; the R^1 group may optionally be substituted with 1, 2, 3 or 4
- 25 substituents, which can be any of the R^3 or R^1 groups or alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxy carbonylamino, aryloxy carbonylamino,
- 30

heteroaryloxylcarbonylamino, uriedo (where the
 uriedo nitrogens may optionally be substituted with
 alkyl, aryl or heteroaryl), heterocyclylcarbonyl-
 amino (where the heterocycle is connected to the
 5 carbonyl group via a nitrogen or carbon atom),
 alkylsulfonylamino, arylsulfonylamino,
 heteroarylsulfonylamino,



10

where J is: CHR^{23} , $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$, $\text{—}\underset{\text{R}^{24}}{\text{CH}}\text{—}\underset{\text{R}^{25}}{\text{CH}}\text{—}$ or $\text{—}\underset{\text{R}^{24}}{\text{C}}=\underset{\text{R}^{25}}{\text{C}}\text{—}$;

R^{23} , R^{24} and R^{25} are independently hydrogen, alkyl,
 alkenyl, alkynyl, aryl, arylalkyl, heteroaryl,
 heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

15

R^{20} , R^{21} , R^{22} are independently hydrogen,
 halo, alkyl, alkenyl, alkoxy, aryloxy, aryl,
 arylalkyl, alkylmercapto, arylmercapto, cycloalkyl,
 cycloalkylalkyl, heteroaryl, heteroarylalkyl,
 hydroxy or haloalkyl; and these substituents may
 20 either be directly attached to R^1 , or attached via
 an alkylene at an open position;

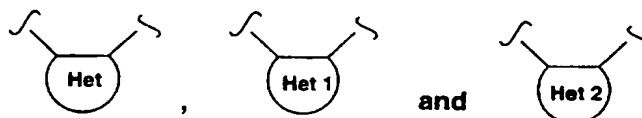
R^2 is independently any of the groups set
 out for R^1 , H, polyhaloalkyl, or cycloheteroalkyl,
 and may be optionally substituted with one to four
 25 of any of the groups defined for R^3 or substituents
 defined for R^1 ;

L^1 is a linking group containing from 1 to
 10 carbons in a linear chain including alkylene,
 alkenylene or alkynylene, which may contain, within
 30 the linking chain any of the following: one or two
 alkenes, one or two alkynes, an oxygen, an amino
 group, an oxo group, and may be substituted with
 one to five alkyl or halo groups;

L^2 may be the same or different from L^1 and may independently be any of the L^1 groups set out above or a single bond;

R^3 , $R^{3'}$, R^4 and $R^{4'}$ may be the same or
 5 different and are independently selected from H, halogen, CF_3 , haloalkyl, hydroxy, alkoxy, alkyl, aryl, alkenyl, alkenyloxy, alkynyl, alkynyloxy, alkanoyl, nitro, amino, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy,
 10 alkoxy carbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, cycloheteroalkyl, cycloheteroalkylalkyl, cyano, Ar-, Ar-alkyl, ArO, Ar-amino, Ar-thio, Ar-sulfinyl, Ar-sulfonyl, Ar-carbonyl, Ar-carbonyloxy or Ar-carbonylamino,
 15 wherein Ar is aryl or heteroaryl and Ar may optionally include 1, 2 or 3 additional rings fused to Ar;

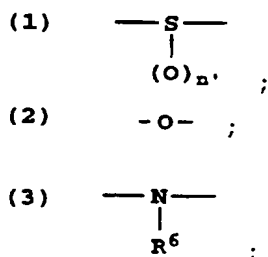
R^{3a} and R^{3b} are the same or different and are independently any of the R^3 groups except
 20 hydroxy, nitro, amino or thio;

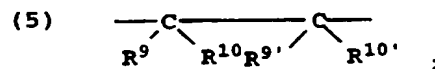
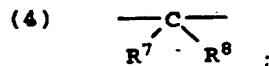


are the same or different and independently represent a 5 or 6 membered heteroaryl ring which
 25 contains 1, 2, 3 or 4 heteroatoms in the ring which are independently N, S or O; and including N-oxides;

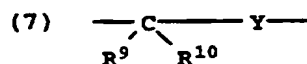
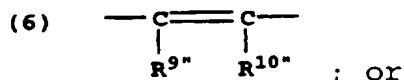
X is a bond, or is one of the following groups:

30





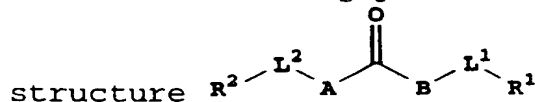
5



wherein

- 10 Y is O, N-R⁶ or S;
 n' is 0, 1 or 2;
 R⁶ is H, lower alkyl, aryl, -C(O)-R¹¹ or
 -C(O)-O-R¹¹;
 R⁷ and R⁸ are the same or different and are
 15 independently H, alkyl, aryl, halogen, -O-R¹², or
 R⁷ and R⁸ together can be oxygen to form a
 ketone;
 R⁹, R¹⁰, R^{9'} and R^{10'} are the same or
 different and are independently H, lower alkyl,
 20 aryl or -O-R¹¹;
 R^{9''} and R^{10''} are the same or different and
 are independently H, lower alkyl, aryl, halogen or
 -O-R¹¹;
 R¹¹ is alkyl or aryl;
 25 R¹² is H, alkyl or aryl;

with the following provisos for compound of the



- (a) when R¹ is unsubstituted alkyl or
 unsubstituted arylalkyl, L¹ cannot contain amino;
 30 (b) when R¹ is alkyl, L¹ cannot contain
 amino and oxo in adjacent positions (to form an
 amido group);
 (c) when R²L²A- is H₂N-, R¹L¹ cannot contain
 amino;

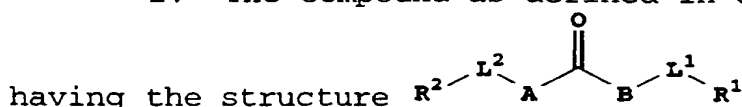
(d) when R^1 is cyano, L^1 must have more than 2 carbons;

(e) R^1L^1 must contain at least 3 carbons;

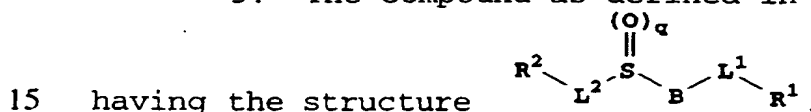
with respect to compounds of formulas I, IA and IB, where R^1 or R^2 is cycloheteroalkyl, R^1 or R^2 is exclusive of 1-piperidinyl, 1-pyrrolidinyl, 1-azetidinyl or 1-(2-oxo-pyrrolidinyl);

with respect to the sulfur containing compounds and alcohols, R^2L^2 cannot have an O or N atom directly attached to $S=(O)_q$ or $CR^x(OH)$, and for IA, R^2L^2 cannot be H.

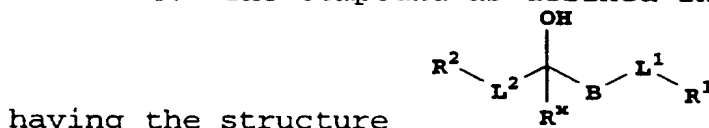
2. The compound as defined in Claim 1



3. The compound as defined in Claim 1



4. The compound as defined in Claim 1



5. The compound as defined in Claim 2 wherein A is a bond.

20 6. The compound as defined in Claim 2 wherein A is -O-.

7. The compound as defined in Claim 2 wherein A is

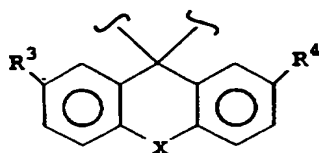
25 8. The compound as defined in Claim 1 wherein B is a fluorenyl-type group.

9. The compound as defined in Claim 1 wherein B is an indenyl-type group.

10. The compound as defined in Claim 1 having the formula



wherein B is



A is NH;

X is a bond, oxygen or sulfur;

R³ and R⁴ are the same or different and are

5 H or F;

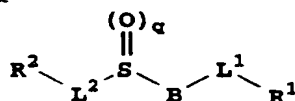
R¹ is aryl, phenyl, heteroaryl, imidazolyl, pyridyl, cyclohexyl, PO(R¹³)(R¹⁴), heteroarylthio, benzimidazolyl, indolyl, benzthiazole-2-thio, imidazole-2-thio, alkyl, alkenyl or 1,3-dioxan-2-yl, wherein each of the above is optionally substituted;

R² is alkyl, polyfluoroalkyl, alkenyl, aryl, phenyl, heteroaryl, imidazolyl or pyridyl, wherein each of the above is optionally substituted;

15 L¹ is a chain containing 1 to 5 atoms in a linear chain;

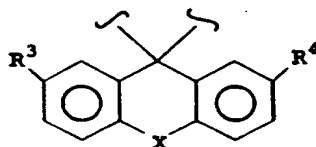
L² is a bond or lower alkylene.

11. The compound as defined in Claim 1 having the formula



20

wherein B is



X is a bond, oxygen or sulfur;

R³ and R⁴ are the same or different and are

25 H or F;

R¹ is aryl, phenyl, heteroaryl, imidazolyl, pyridyl, cyclohexyl, PO(R¹³)(R¹⁴), heteroarylthio, benzimidazolyl, indolyl, benzthiazole-2-thio, imidazole-2-thio, alkyl, alkenyl or 1,3-dioxan-2-yl, wherein each of the above is optionally substituted;

30

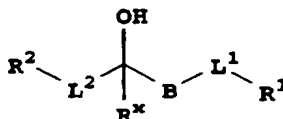
R² is alkyl, polyfluoroalkyl, alkenyl, aryl, phenyl, heteroaryl, imidazolyl or pyridyl, wherein each of the above is optionally substituted;

L¹ is a chain containing 1 to 5 atoms in a linear chain;

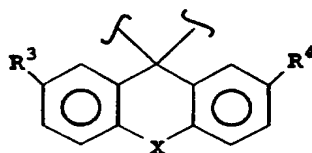
L² is a bond or lower alkylene;

q is 0, 1 or 2.

12. The compound as defined in Claim 1 having the formula



wherein B is



X is a bond, oxygen or sulfur;

R³ and R⁴ are the same or different and are H or F;

R¹ is aryl, phenyl, heteroaryl, imidazolyl, pyridyl, cyclohexyl, PO(R¹³)(R¹⁴), heteroarylthio, benzimidazolyl, indolyl, benzthiazole-2-thio, imidazole-2-thio, alkyl, alkenyl or 1,3-dioxan-2-yl, wherein each of the above is optionally substituted;

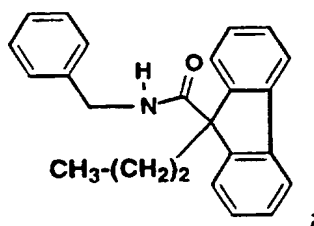
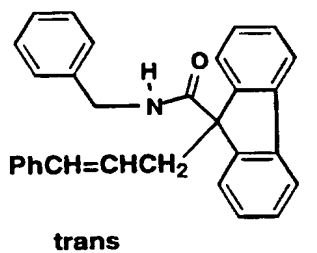
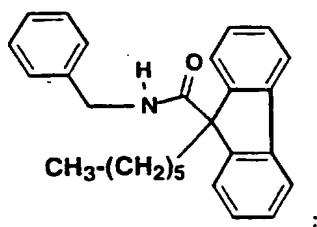
R² is alkyl, polyfluoroalkyl, alkenyl, aryl, phenyl, heteroaryl, imidazolyl or pyridyl, wherein each of the above is optionally substituted;

L¹ is a chain containing 1 to 5 atoms in a linear chain;

L² is a bond or lower alkylene;

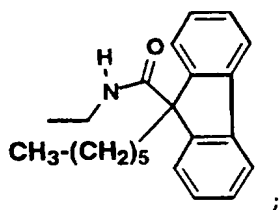
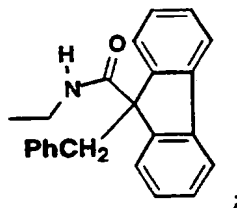
R^x is H.

13. The compound as defined in Claim 1 which is N-(phenylmethyl)-9-(3-phenylpropyl)-9H-fluorene-9-carboxamide;

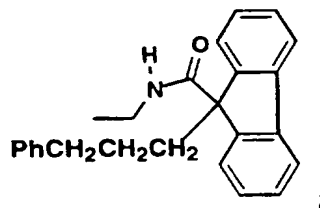


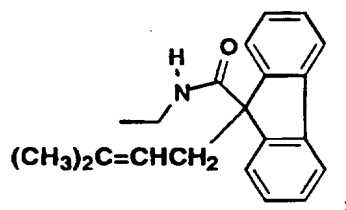
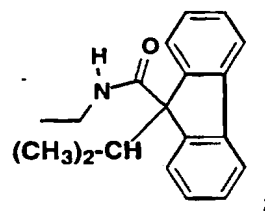
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(E)-N-ethyl-9-(3-phenyl-2-propenyl)-9H-fluorene-9-carboxamide;



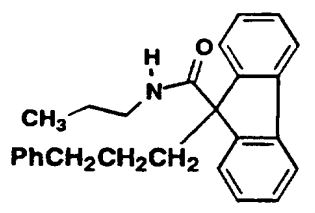
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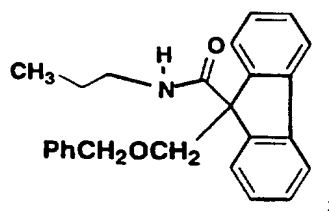
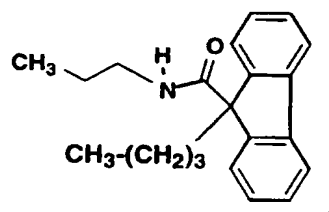


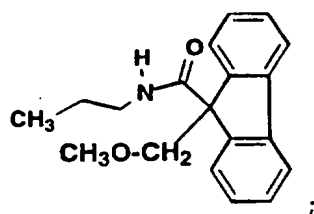
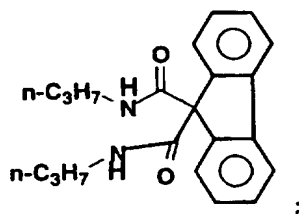
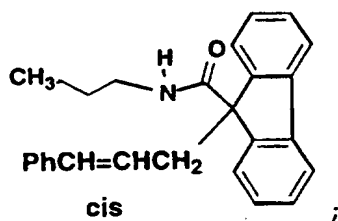
9-[4-(dibutoxyphosphinyl)butyl]-N-propyl-
 5 9H-fluorene-9-carboxamide;

(E)-9-(3-phenyl-2-propenyl)-N-propyl-9H-
 fluorene-9-carboxamide;

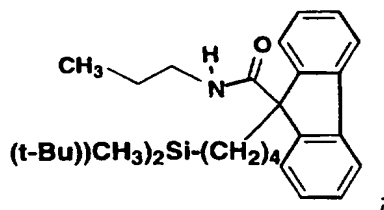
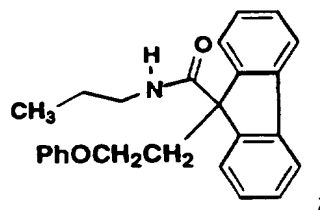


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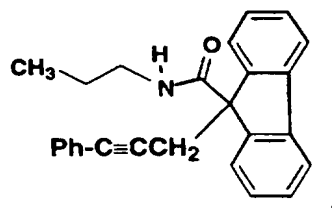


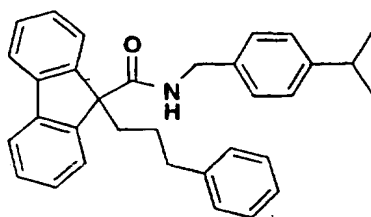


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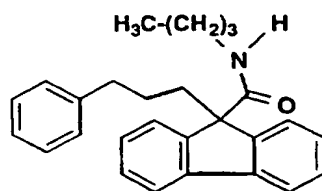


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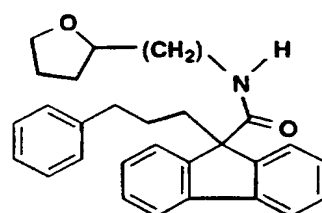




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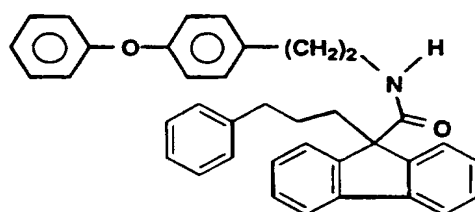


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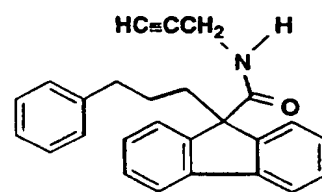


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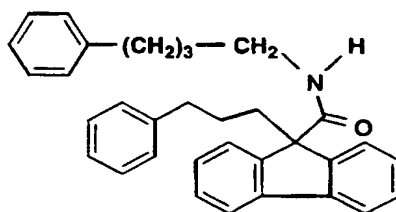


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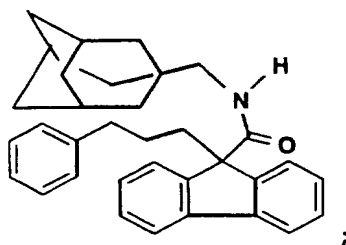
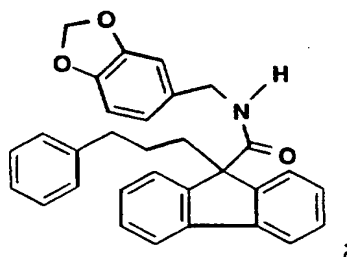
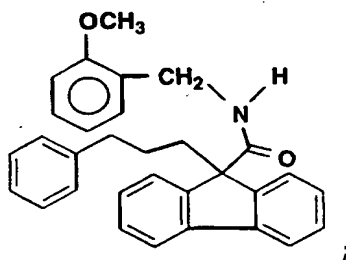


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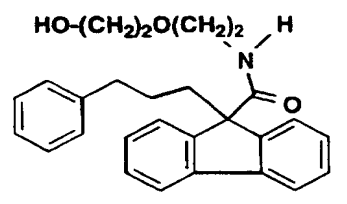
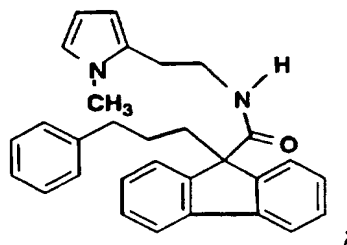
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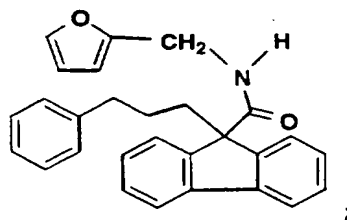
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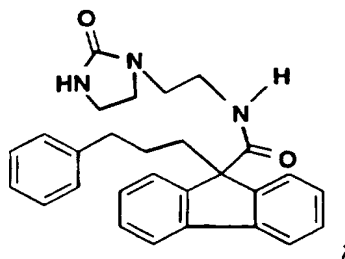
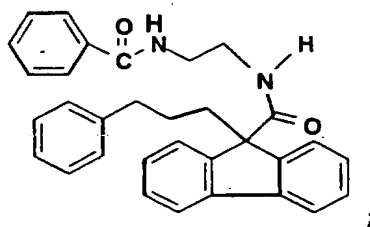


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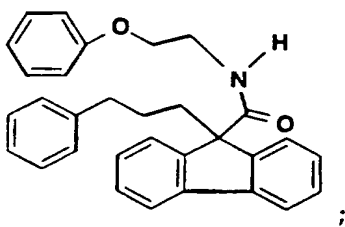
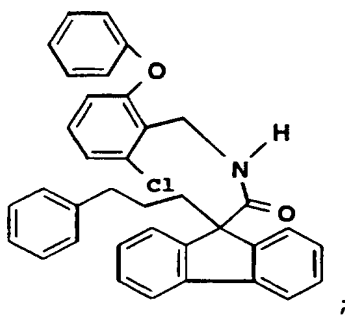


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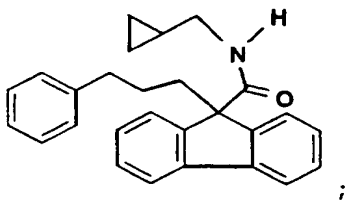


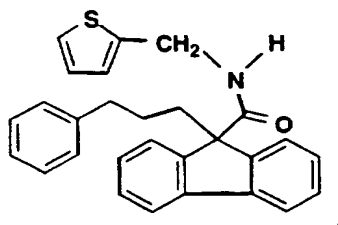
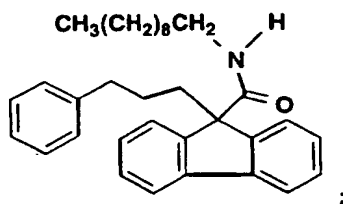
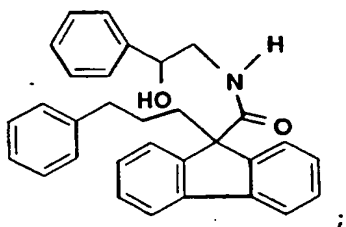


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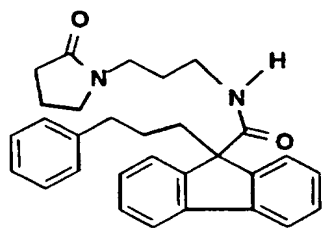
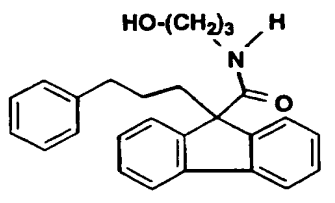


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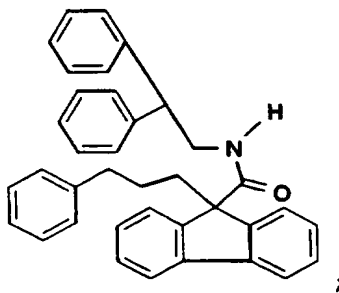


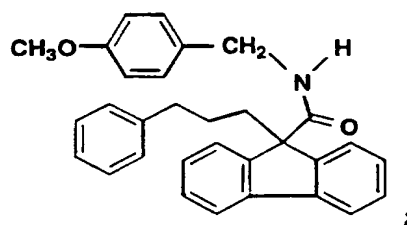
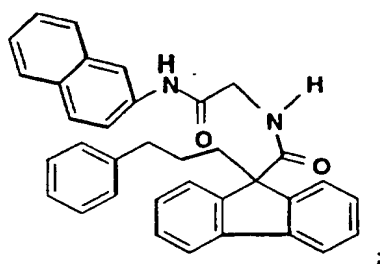
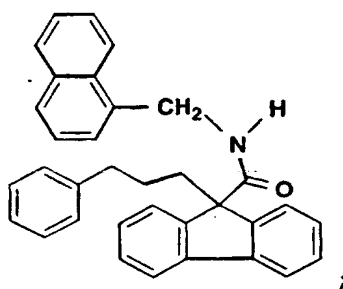


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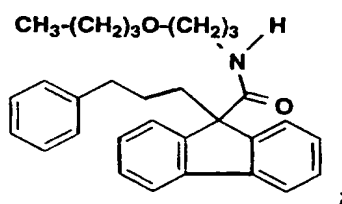
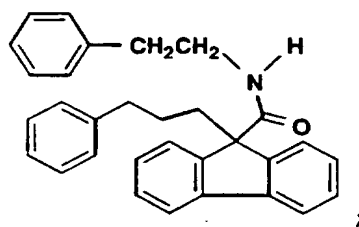


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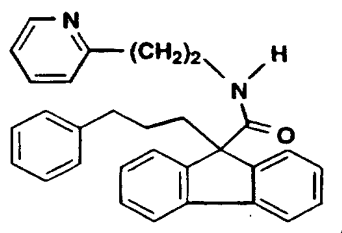


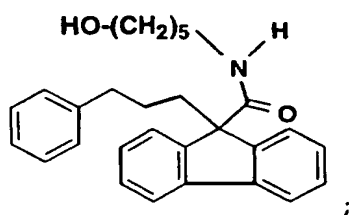
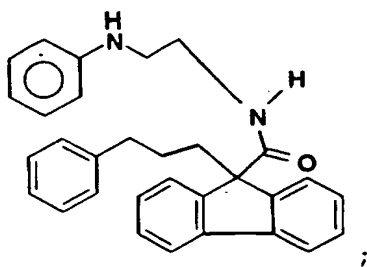


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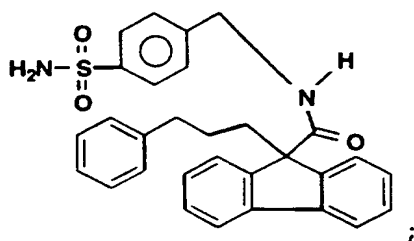
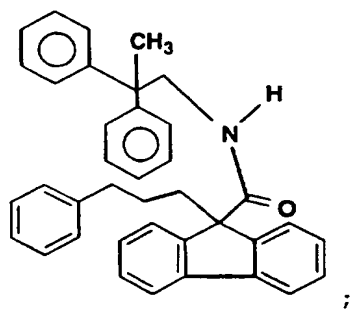


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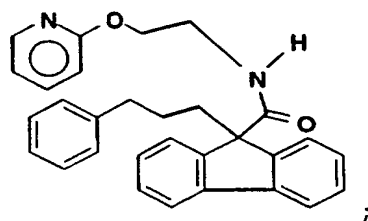


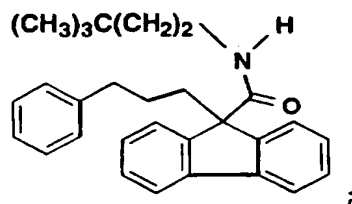
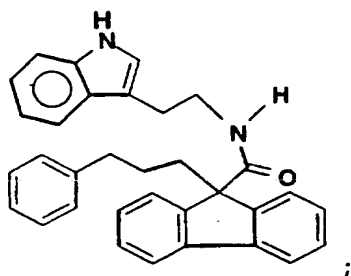


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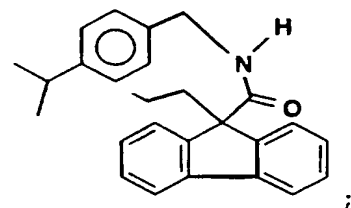
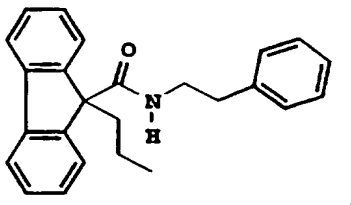


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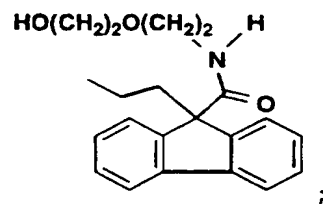
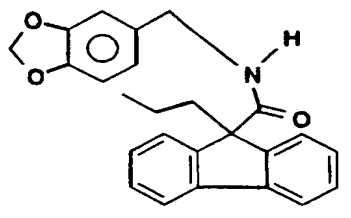


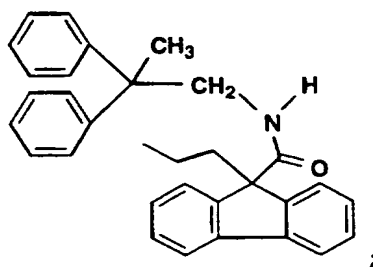
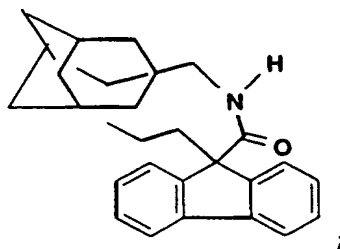
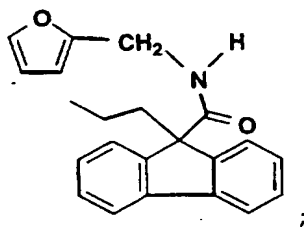


9-(3-phenylpropyl)-N-(2,2,2-trifluoro-
5 ethyl)-9H-fluorene-9-carboxamide;

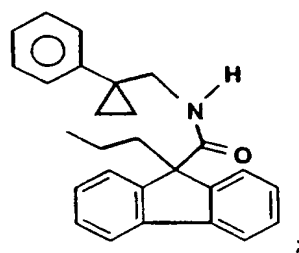
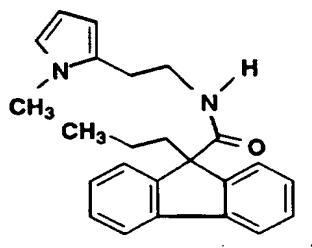


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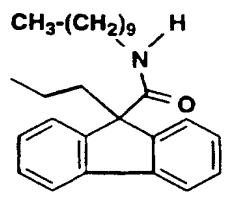
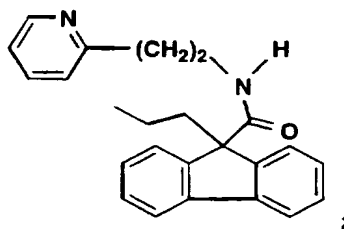
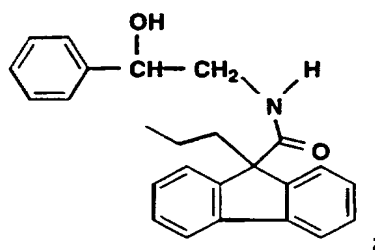
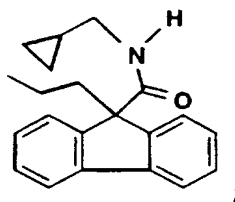
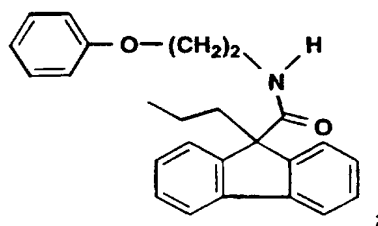
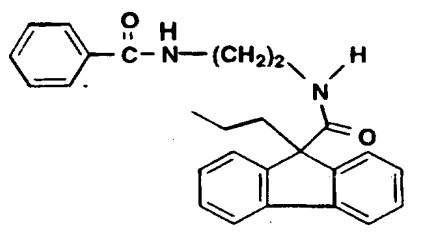


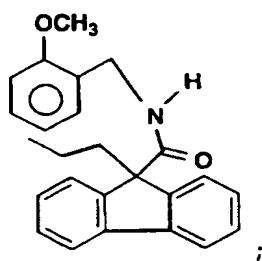
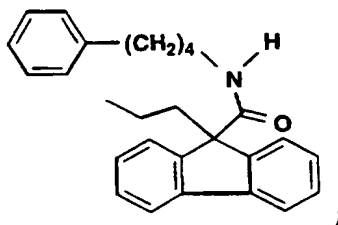
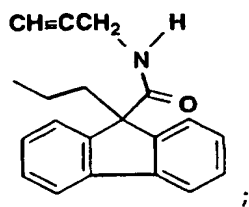


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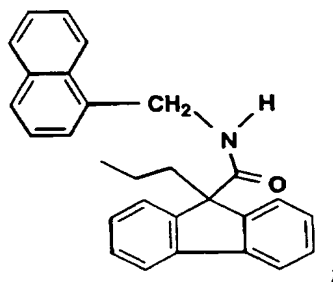
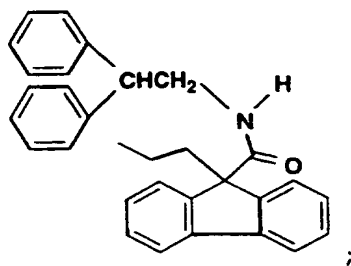


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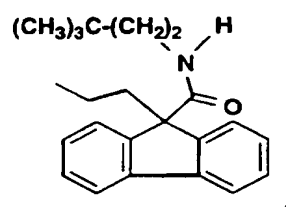
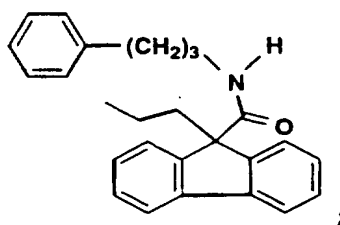
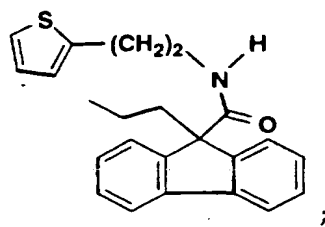




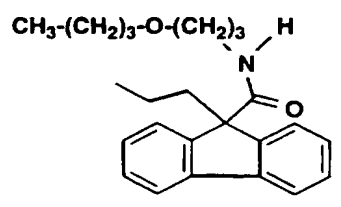
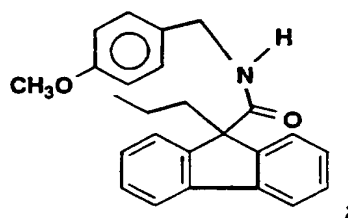
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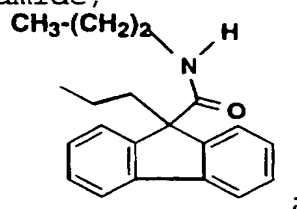


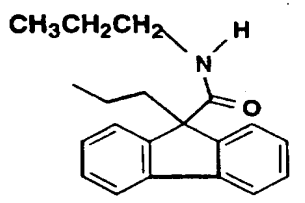
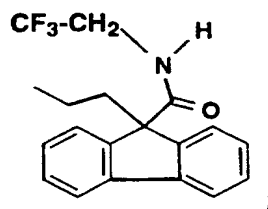
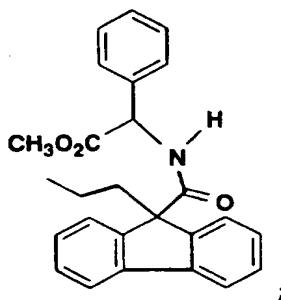
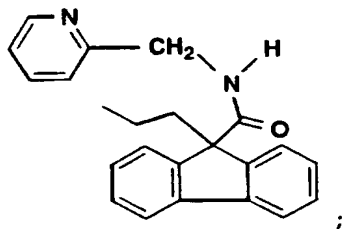
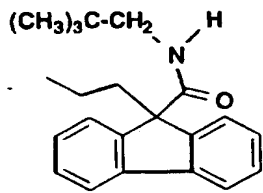
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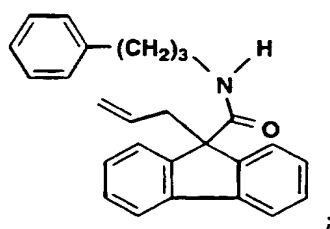
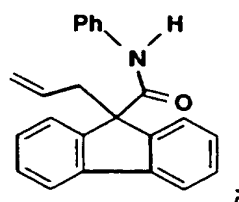
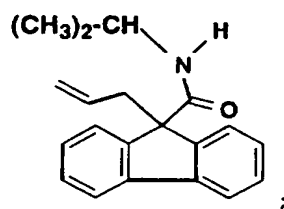
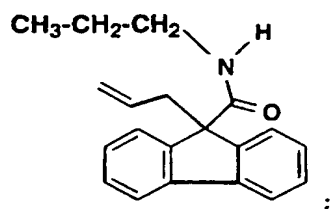
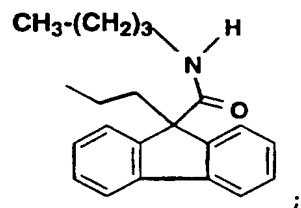
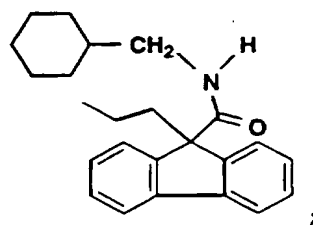
N-methyl-N-(phenylmethyl)-9-propyl-9H-fluorene-9-carboxamide;

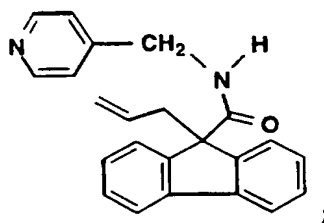
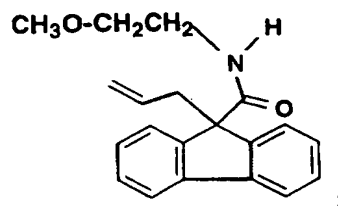
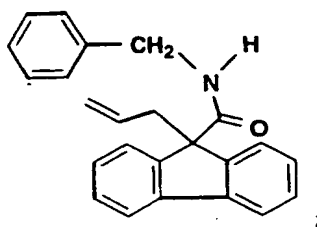




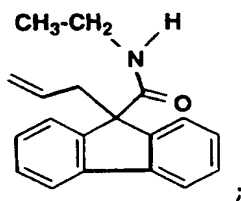
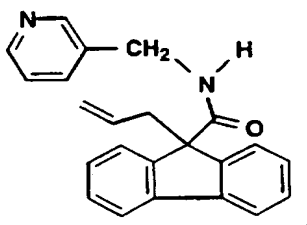
- 5
- 10 9-(2-propenyl)-N-(2-pyridinylmethyl)-9H-fluorene-9-carboxamide;
 N-butyl-9-(2-propenyl)-9H-fluorene-9-carboxamide;
 9-[[2,2-bis(trifluoromethyl)-1,3-dioxolan-
 15 4-yl]methyl]-N-ethyl-9H-fluorene-9-carboxamide;
 9-(2,3-dihydroxypropyl)-N-ethyl-9H-fluorene-9-carboxamide;

9-(3-phenylpropyl)-N-(3-hydroxy)propyl-9H-xanthene-9-carboxamide;



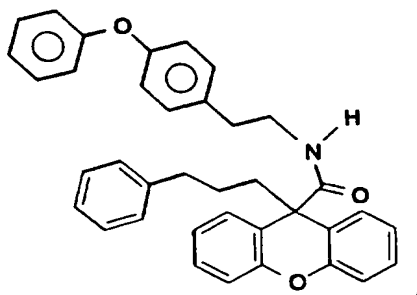


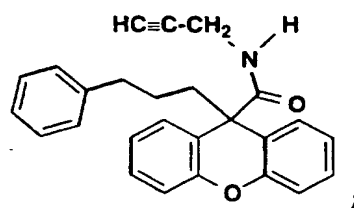
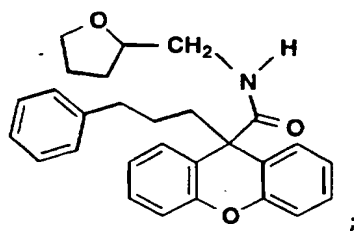
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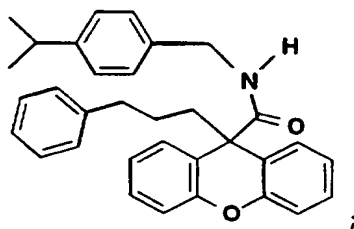
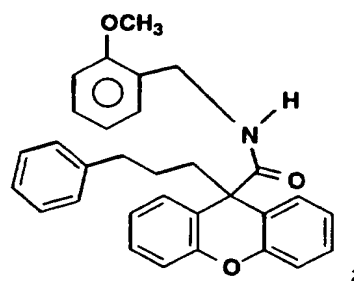
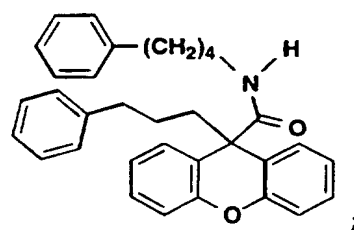
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9-(1-piperidinylcarbonyl)-9-(2-propenyl)-
9H-fluorene;

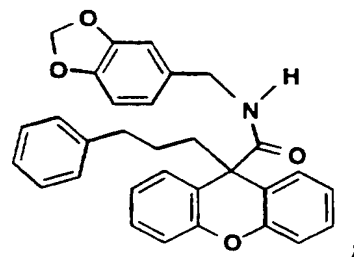


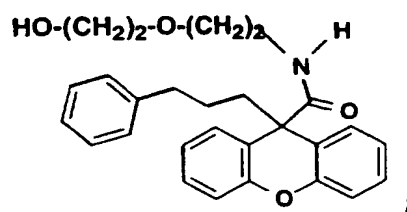
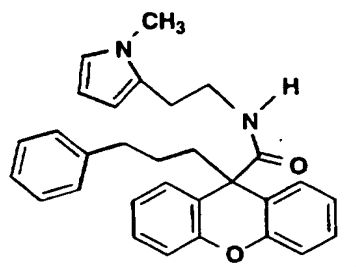
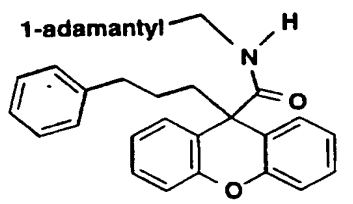


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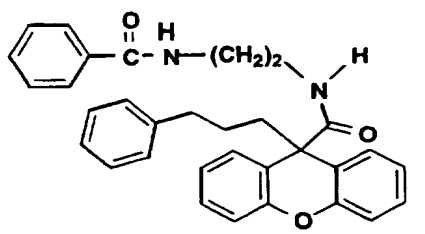
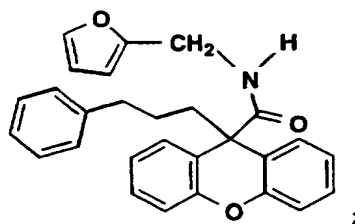


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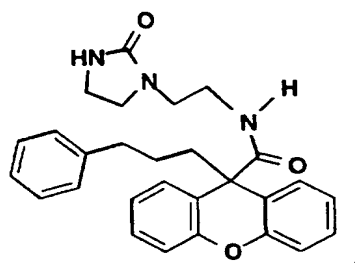


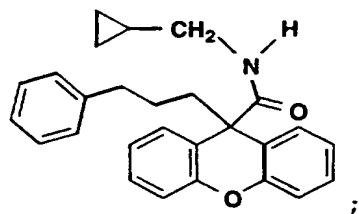
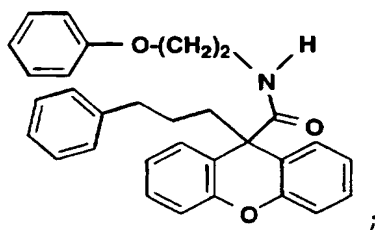
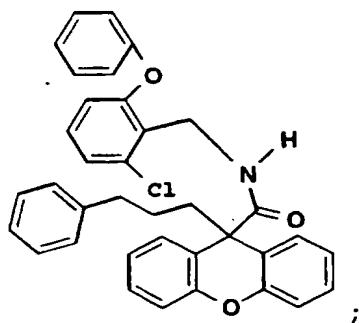


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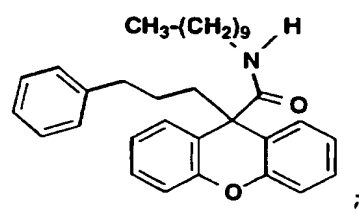
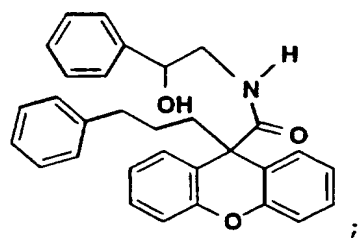


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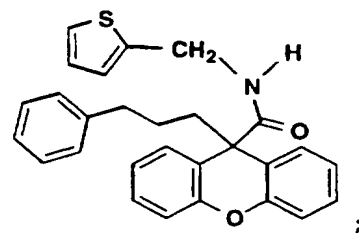


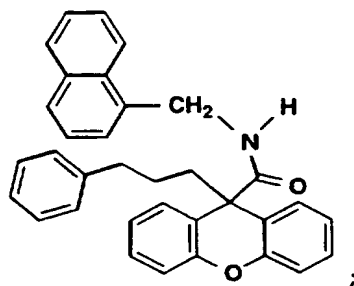
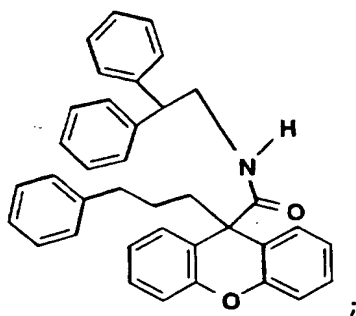
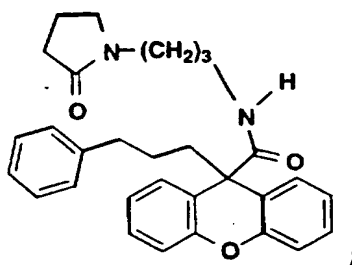


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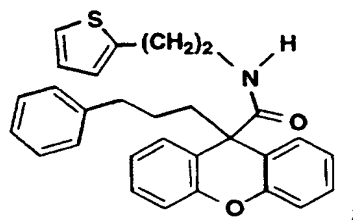
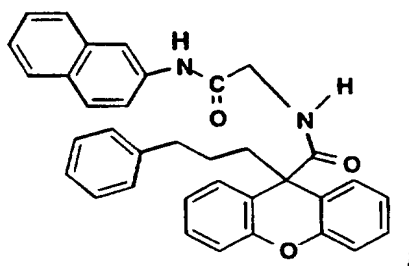


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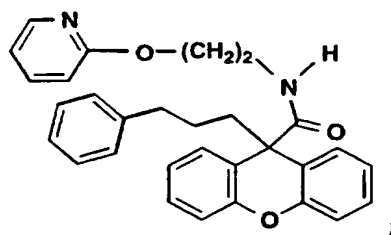
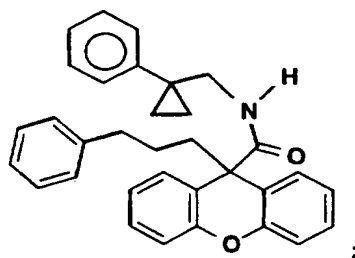
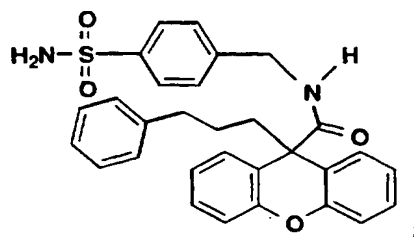




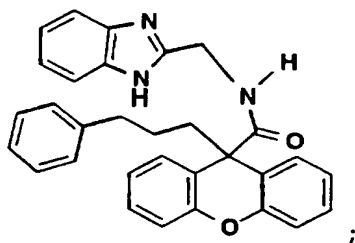
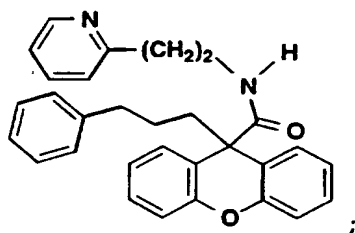
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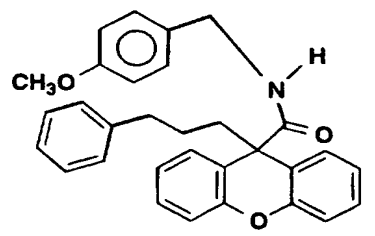
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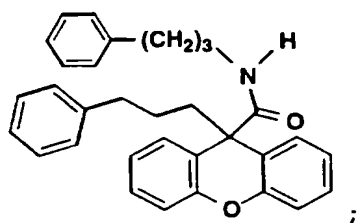
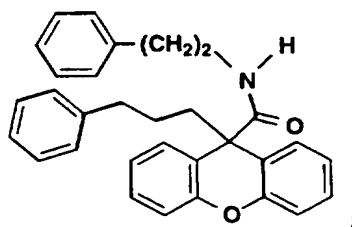
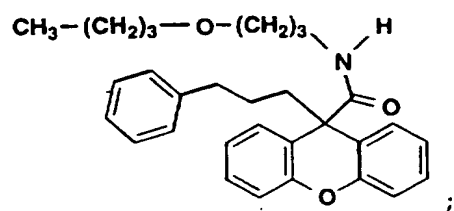


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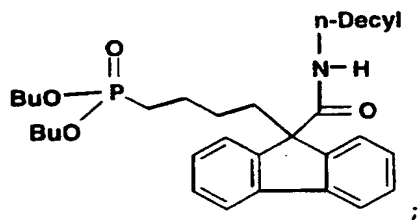
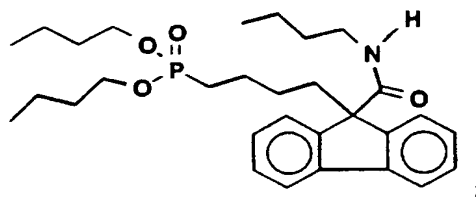


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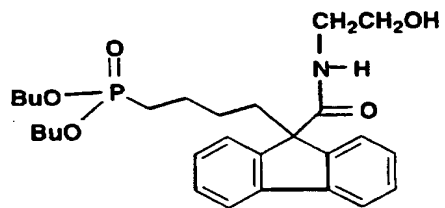


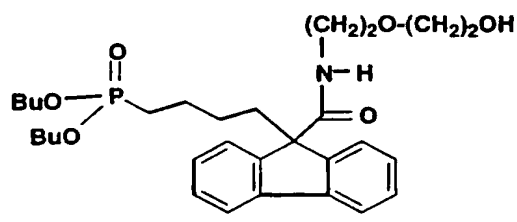
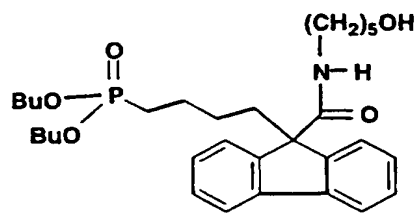
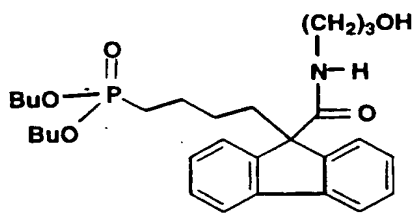


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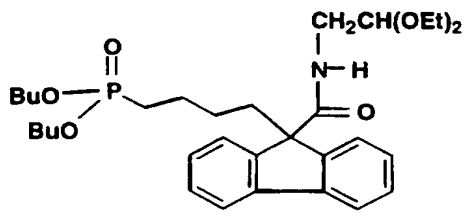
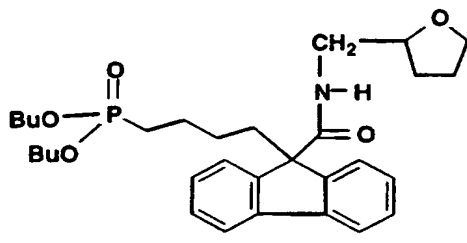


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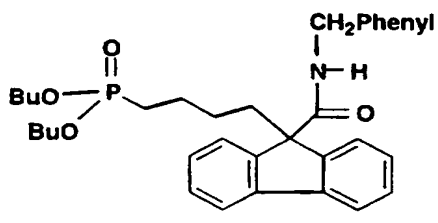


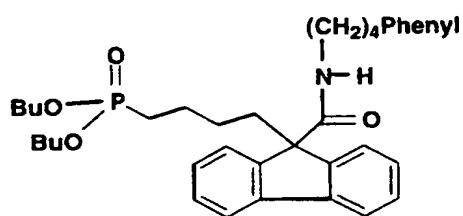
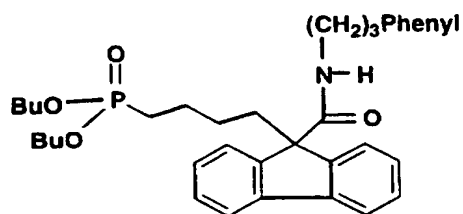
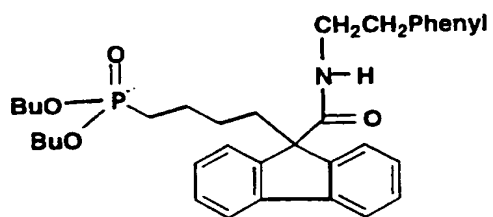


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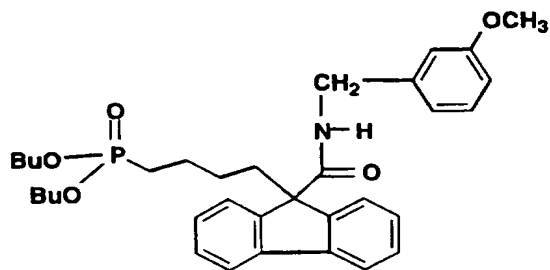
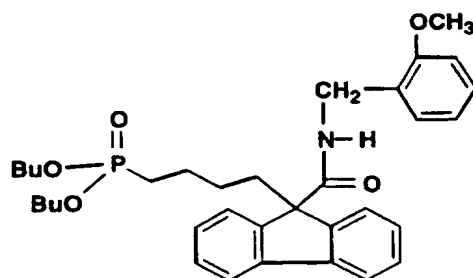


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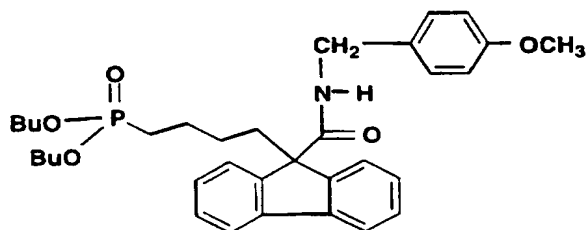


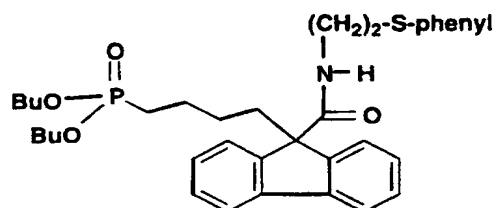
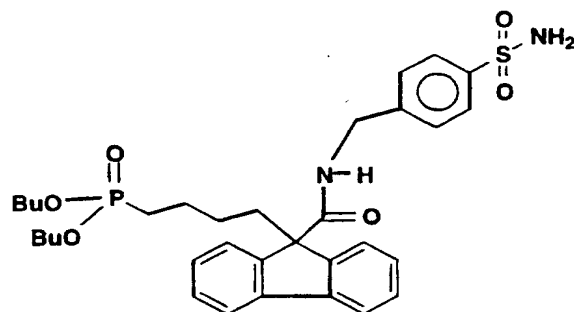
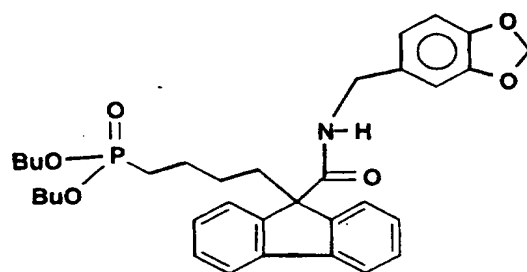


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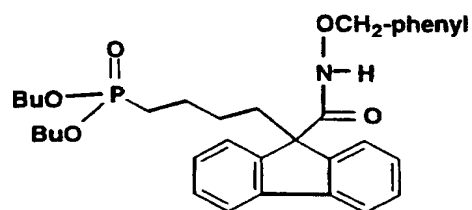
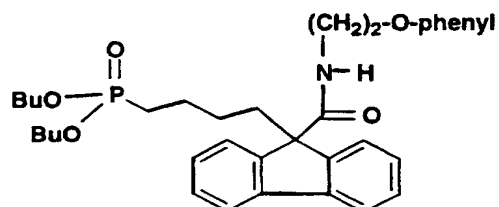


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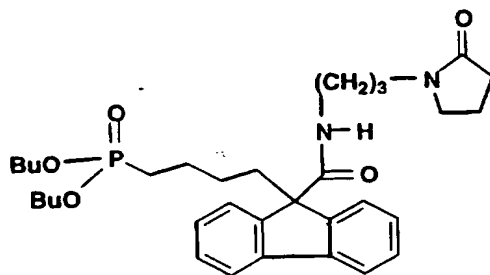




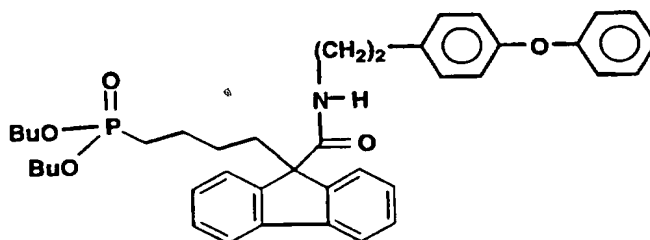
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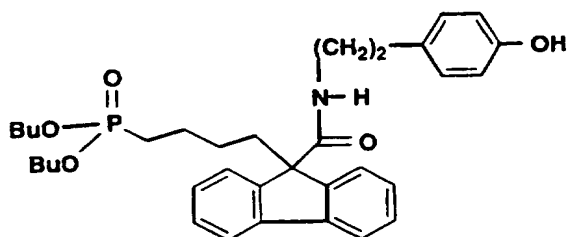
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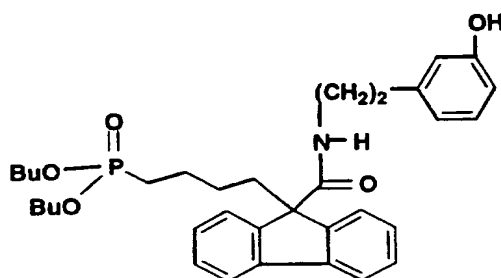


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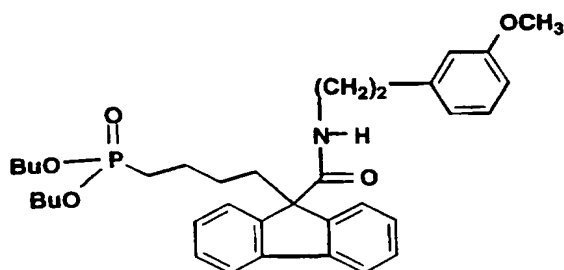


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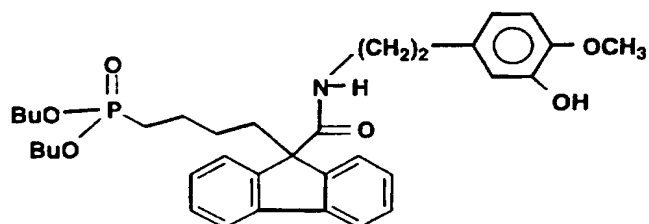
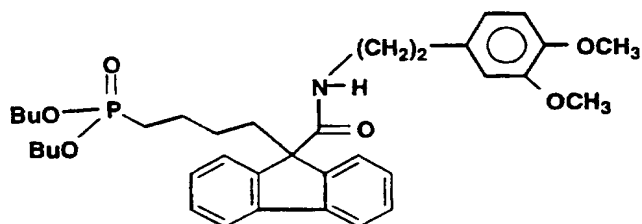
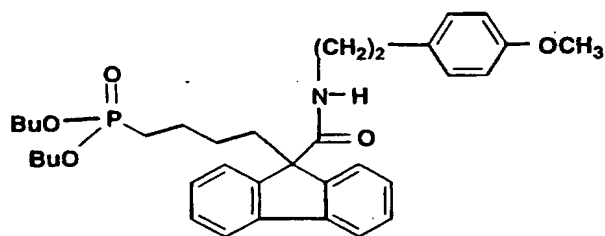


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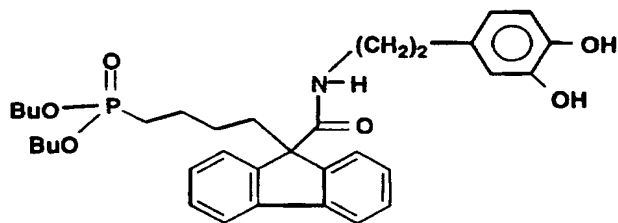
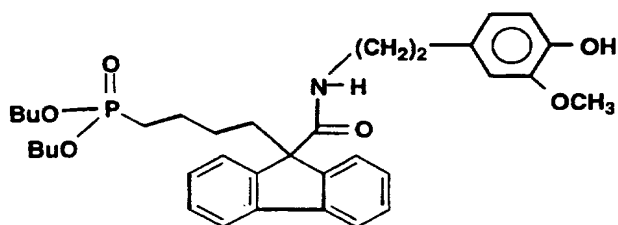


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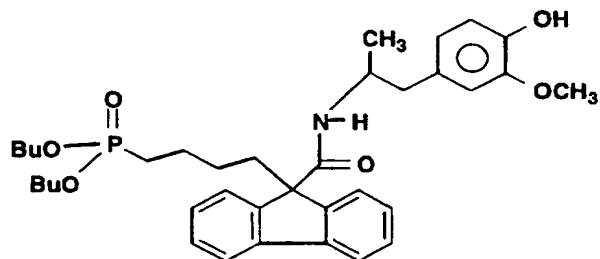
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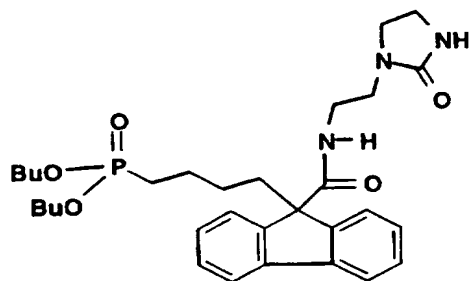
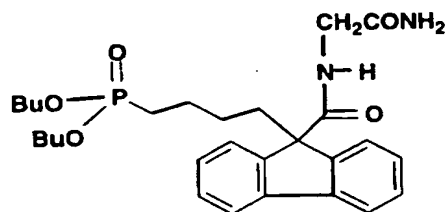
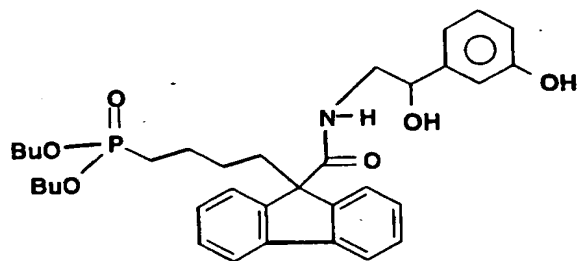


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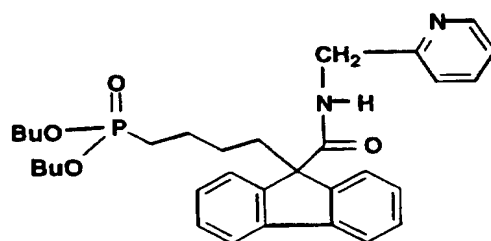
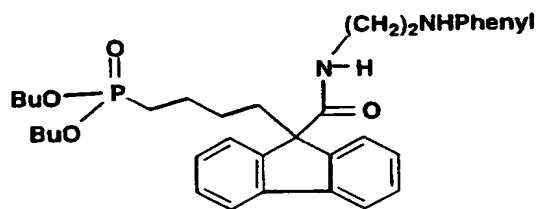


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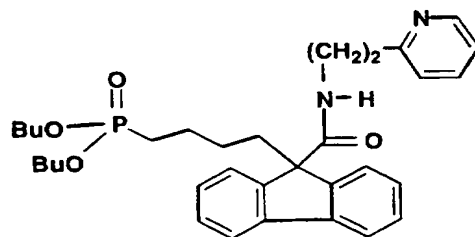


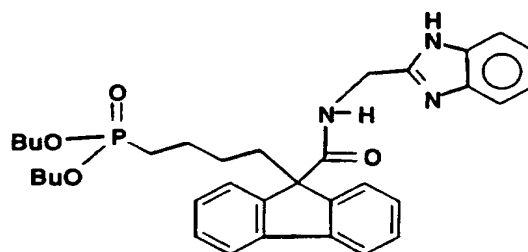
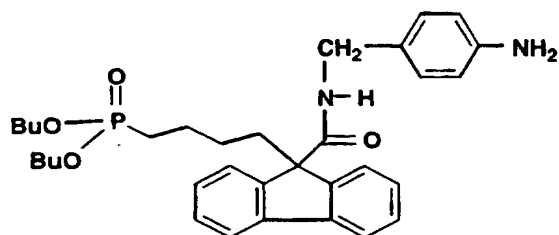
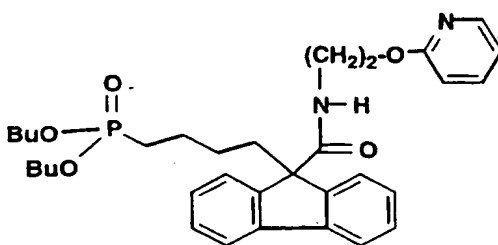


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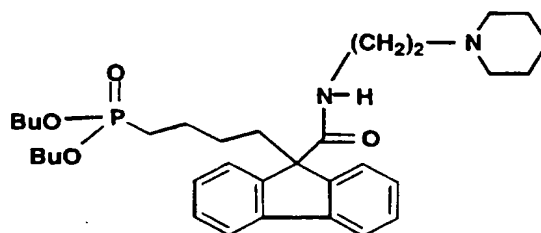
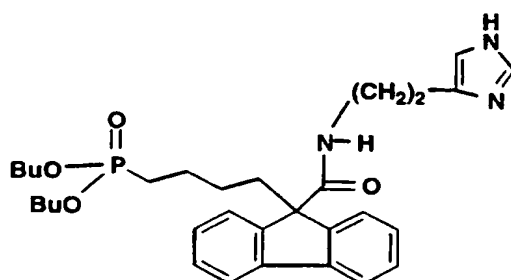


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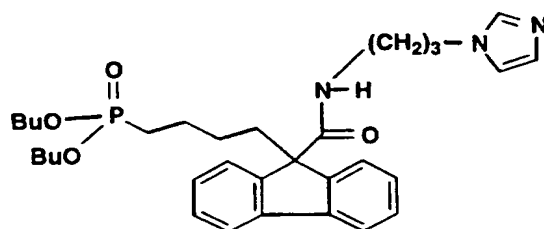
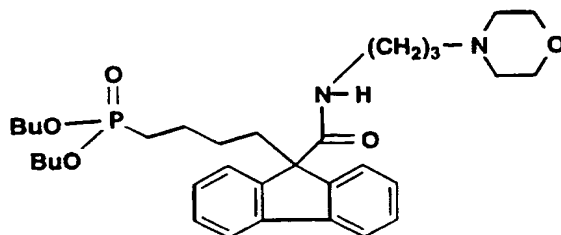
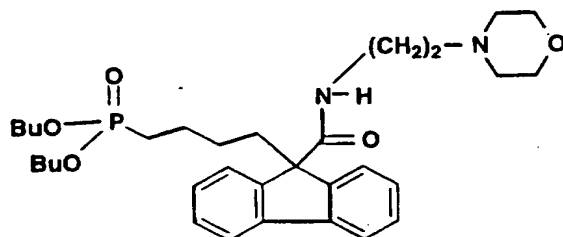




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9-[4-(dibutoxyphosphinyl)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

9-(2-propenyl)-9H-fluorene-9-carboxylic acid, ethyl ester;

9-propyl-9H-fluorene-9-carboxaldehyde;

9-(4-cyanobutyl)-N-propyl-9H-fluorene-9-carboxamide;

1-[9-(3-phenylpropyl)-9H-fluorene-9-yl]-1-butanone;

9-(3-phenylpropyl)- α -propyl-9H-fluorene-9-methanol;

4-hydroxy-1-(9-propyl-9H-fluorene-9-yl)-butanone;

20 N-[3-(dibutoxyphosphinyl)propyl]-9-propyl-9H-fluorene-9-carboxamide;

N-[5-(dibutoxyphosphinyl)pentyl]-9-propyl-9H-fluorene-9-carboxamide;

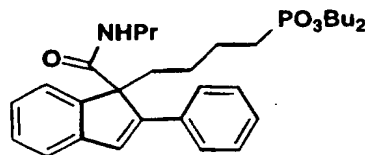
- N-[[4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)phenyl]methyl]-9-propyl-9H-fluorene-9-carboxamide;
- (E)-9-[4-(dibutoxyphosphinyl)-2-butenyl]-2,7-difluoro-N-propyl-9H-fluorene-9-carboxamide;
- 5 9-[4-(dibutoxyphosphinyl)butyl]-2,7-difluoro-N-propyl-9H-fluorene-9-carboxamide;
- 9-[4-(diethoxyphosphinyl)butyl]-N-propyl-9H-fluorene-9-carboxamide;
- 10 9-[4-(diphenylphosphinyl)butyl]-N-propyl-9H-fluorene-9-carboxamide;
- [4-[9-(butylthio)-9H-fluoren-9-yl]butyl]-phosphonic acid, dibutyl ester;
- [4-[9-(butylsulfonyl)-9H-fluoren-9-yl]butyl]-phosphinic acid, dibutyl ester;
- 15 [4-[9-(butylsulfinyl)-9H-fluoren-9-yl]butyl]-phosphonic acid, dibutyl ester;
- 5-[4-(dibutoxyphosphinyl)butyl]-N-propyl-5H-indeno[1,2-b]pyridine-5-carboxamide;
- 20 (E)-9-[4-(dibutoxyphosphinyl)-2-butenyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
- 9-[4-[4-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)phenyl]butyl]-N-propyl-9H-fluorene-9-
- 25 carboxamide;
- 9-[4-[4-[(2-phenoxyphenyl)carbonyl]amino]phenyl]butyl]-N-propyl-9H-fluorene-9-carboxamide;
- 9-[4-[4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-phenyl]butyl]-N-propyl-9H-fluorene-9-
- 30 carboxamide;
- 9-[3-[4-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)phenyl]propyl]-N-propyl-9H-fluorene-9-carboxamide;
- 9-[3-[4-(benzoylamino)]phenyl]-N-propyl-9H-
- 35 fluorene-9-carboxamide;
- 9-[3-[(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-phenyl]propyl]-N-propyl-9H-fluorene-9-carboxamide;

- 9-[5-[(6-ethoxy-2-benzothiazolyl)thio]-
pentyl]-N-propyl-9H-fluorene-9-carboxamide;
9-[4-[4-(benzoylamino)phenyl]butyl]-N-
propyl-9H-fluorene-9-carboxamide;
5 9-[5-(dibutoxyphosphinyl)pentyl]-N-propyl-
9H-fluorene-9-carboxamide;
N,N-diethyl-9-(2-propenyl)-9H-fluorene-9-
carboxamide;
N-ethyl-9-propyl-9H-fluorene-9-carboxamide;
10 N-ethyl-9-(2-propenyl)-9H-xanthene-9-
carboxamide;
N-ethyl-9-(3-phenylpropyl)-9H-xanthene-9-
carboxamide;
9-[(4-morpholinyl)carbonyl]-9-propyl-9H-
15 fluorene;
9-hexyl-N-propyl-9H-xanthene-9-carboxamide;
N-methoxy-N-methyl-9-propyl-9H-fluorene-9-
carboxamide;
10,11-dihydro-5-(3-phenyl-2-propenyl)-N-
20 propyl-5H-dibenzo[a,d]cycloheptene-5-carboxamide;
N-methyl-9-propyl-9H-fluorene-9-
carboxamide;
1-(9-propyl-9H-fluorene-9-yl)-1-pentanone;
 α -butyl-9-propyl-9H-fluorene-9-methanol;
25 1-(9-propyl-9H-fluorene-9-yl)-1-butanone;
 α ,9-dipropyl-9H-fluorene-9-methanol;
10,11-dihydro-5-(2-propenyl)-N-propyl-5H-
dibenzo-[a,d]cycloheptene-5-carboxamide;
9-(3-phenylpropyl)-N-propyl-9H-
30 thioxanthene-9-carboxamide;
N,9-dipropyl-9H-thioxanthene-9-carboxamide;
10,11-Dihydro-5-(3-phenylpropyl)-N-propyl-5H-
dibenzo-[a,d]cycloheptane-5-carboxamide;
(E)-2,7-difluoro-9-(3-phenyl-2-propenyl)-N-
35 propyl-9H-fluorene-9-carboxamide;
9-(3-phenylpropyl)-N-(2-pyridinylmethyl)-
9H-fluorene-9-carboxamide;

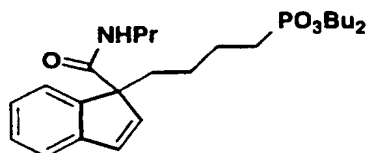
- 2,7-difluoro-9-(3-phenylpropyl)-N-propyl-9H-fluorene-9-carboxamide;
- 2,7-difluoro-9-(3-phenylpropyl)-N-(4-pyridinylmethyl)-9H-fluorene-9-carboxamide;
- 5 9-(butylthio)-9-propyl-9H-fluorene;
- 9-(butylsulfinyl)-9-propyl-9H-fluorene;
- 9-(4-hydroxybutyl)-N-propyl-9H-fluorene-9-carboxamide;
- 9-[4-(phenylthio)butyl]-N-propyl-9H-fluorene-9-carboxamide;
- 10 9-[3-(1,3-dioxan-2-yl)propyl]-N-propyl-9H-fluorene-9-carboxamide;
- 9-[3-(1,3-dioxolan-2-yl)propyl]-N-propyl-9H-fluorene-9-carboxamide;
- 15 cis-N,9-dipropyl-1H-thioxanthene-9-carboxamide, 10-oxide;
- 5-(2-propenyl)-N-propyl-5H-indeno[1,2-b]pyridine-5-carboxamide;
- (E)-5-(3-phenyl-2-propenyl)-N-propyl-5H-indeno[1,2-b]pyridine-5-carboxamide;
- 20 N-ethyl-N-methyl-9-(2-propenyl)-9H-fluorene-9-carboxamide;
- N,9-dipropyl-9H-thioxanthene-9-carboxamide, 10,10-dioxide;
- 25 trans-N,9-dipropyl-9H-thioxanthene-9-carboxamide, 10-oxide;
- 9-[3-(dibutoxyphosphinyl)propyl]-N-(2-pyridinylmethyl)-9H-fluorene-9-carboxamide;
- 1-(9-propyl-9H-fluorene-9-yl)-2-(1-piperidinyl)ethanone, monohydrochloride;
- 30 N-(5-hydroxypentyl)-9-propyl-9H-fluorene-9-carboxamide;
- 9-(3-cyanopropyl)-N-propyl-9H-fluorene-9-carboxamide;
- 35 N-[[4-[(9-propyl-9H-fluorene-9-yl)carbonyl]-amino]phenyl]methyl]-9-propyl-9H-fluorene-9-carboxamide;

- N-[4-(4-aminophenyl)methyl]-9-propyl-9H-fluorene-9-carboxamide;
9-[3-(dibutoxyphosphinyl)propyl]-N-propyl-9H-fluorene-9-carboxamide;
5 4-(1-piperidinyl)-1-(9-propyl-9H-fluorene-9-yl)-1-butanone, monohydrochloride;
N-methyl-9-(3-phenylpropyl)-9H-fluorene-9-carboxamide;
2-(dimethylamino)-9-(3-phenylpropyl)-N-propyl-9H-fluorene-9-carboxamide;
10 9-[4-(dibutoxyphosphinyl)-2-butenyl]-N-propyl-9H-fluorene-9-carboxamide;
9-[4-(4-nitrophenyl)butyl]-N-propyl-9H-fluorene-9-carboxamide;
15 9-[3-(4-nitrophenyl)-2-propenyl]-N-propyl-9H-fluorene-9-carboxamide;
5-(3-phenylpropyl)-N-propyl-5H-indeno[1,2-b]pyridine-5-carboxamide;
9-[4-(4-aminophenyl)butyl]-N-propyl-9H-fluorene-9-carboxamide;
20 9-[3-(4-aminophenyl)propyl]-N-propyl-9H-fluorene-9-carboxamide;
9-[4-(dibutoxyphosphinyl)butyl]-9H-fluorene-9-carboxylic acid, methyl ester;
25 N,N-dibutyl-9-[(propylamino)carbonyl]-9H-fluorene-9-butanamide;
9-(5-cyanopentyl)-N-propyl-9H-fluorene-9-carboxamide;
9-[2-[[[4-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)phenyl]sulfonyl]amino]ethyl]-N-(2,2,2-trifluoro-ethyl)-9H-fluorene-9-carboxamide;
30 (Z)-9-[4-[(6-ethoxy-2-benzothiazolyl)thio]-2-butenyl]-N-propyl-9H-fluorene-9-carboxamide;
9-[4-(dibutoxyphosphinyl)butyl]-N-(2,2,2-trifluoropropyl)-9H-xanthene-9-carboxamide;
35

9-[4-[butoxy[2-(4-morpholinyl)ethoxy]phosphinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;



5 9-[4-(dibutoxyphosphinyl)butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;



10 (E)-9-[4-(dibutoxyphosphinyl)-2-butenyl]-N-propyl-9H-fluorene-9-carboxamide;

9-[4-[4-(benzoylamino)-1H-imidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

15 9-[4-[5-(benzoylamino)-2-pyridinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

9-[4-[4-[(2-phenoxybenzoyl)amino]-1H-imidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

20 9-[4-[(2-bromo-5-pyridinyl)amino]butyl]-N-propyl-9H-fluorene-9-carboxamide;

9-[2-[[[4-(benzoylamino)phenyl]sulfonyl]amino]ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

25 9-(4-phenylbutyl)-N-propyl-9H-fluorene-9-carboxamide;

3-(9-propyl-9H-fluorene-9-yl)sulfonyl]propanoic acid, methyl ester;

9-[4-[(6-ethoxy-2-benzothiazolyl)thio]butyl]-N-propyl-9H-fluorene-9-carboxamide;

30 9-[3-[(6-ethoxy-2-benzothiazolyl)thio]propyl]-N-propyl-9H-fluorene-9-carboxamide;

- (Z)-9-[4-(diethoxyphosphinyl)-2-butenyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
9-[4-(diethoxyphosphinyl)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
5 9-[4-(dibutoxyphosphinyl)butyl]-N-(2,2,3,3,3-pentafluoropropyl)-9H-fluorene-9-carboxamide;
9-[4-(dibutoxyphosphinyl)butyl]-N-propyl-9H-xanthene-9-carboxamide;
10 9-[4-(dibutoxyphosphinyl)butyl]-N-(2,2,3,3,4,4,4-heptafluorobutyl)-9H-fluorene-9-carboxamide;
9-[4-(dibutoxyphosphinyl)butyl]-N-propyl-9H-indeno-[2,1-b]pyridine-9-carboxamide;
15 9-[4-[4-[(phenylsulfonyl)amino]phenyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
[4-[9-(1-oxopentyl)-9H-fluoren-9-yl]butyl]-phosphonic acid;
20 9-[5-(dibutoxyphosphinyl)pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
9-[3-[[5-[(2-phenoxybenzoyl)amino]-2-pyridinyl]oxy]propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
25 [6-[9-[(2,2,2-trifluoroethyl)amino]-carbonyl]-9H-fluoren-9-yl]hexyl]phosphonic acid, dibutyl ester;
9-[4-[5-[(2-phenoxybenzoyl)amino]-2-pyridinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
30 9-[4-[4-(benzoylamino)-2-methyl-1H-imidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
9-[4-[4-[(2-phenoxybenzoyl)amino]-2-methyl-1H-imidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
35 1H-imidazol-1-yl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

- 9-[3-[[2-(benzoylamino)-5-pyridinyl]amino]-propyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
- 5 [[4-(benzoylamino)phenyl]methyl][2-[9-[[2,2,2-trifluoroethyl]amino]carbonyl]-9H-fluorene-9-yl]ethyl]carbamic acid, 1,1-dimethylethyl ester;
- 9-[2-[[4-(benzoylamino)phenyl]methyl]-amino]-ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
- 10 9-[4-[butoxy(tetrahydrofuran-2-ylmethoxy)-phosphinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
- 9-[4-[butoxy(2-pyridinylmethoxy)-phosphinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-
- 15 fluorene-9-carboxamide;
- 9-[4-(dipropoxyphosphinyl)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
- 9-[4-[4-[[4-(nitrophenyl)sulfonyl]amino]-phenyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-
- 20 9-carboxamide;
- 9-[4-[4-[[2-(nitrophenyl)sulfonyl]-amino]phenyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
- 9-[4-(dibutoxyphosphinyl)butyl]-3,6-
- 25 difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
- 9-[3-[[5-[(2-phenoxybenzoyl)amino]-2-pyridinyl]oxy]propyl]-N-propyl-9H-fluorene-9-carboxamide;
- 30 9-[6-[(6-ethoxy-2-benzothiazolyl)thio]-hexyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
- 4-[9-[[2,2,2-trifluoroethyl]amino]-carbonyl]-9H-fluorene-9-yl]butyl]phosphonic acid,
- 35 di(1-methyl-ethyl)ester;
- [[4-[(2-phenoxybenzoyl)amino]phenyl]-methyl][2-[9-[[2,2,2-trifluoroethyl]amino]-

carbonyl]-9H-fluorene-9-yl]ethyl]carbamic acid, 1,1-dimethylethyl ester;

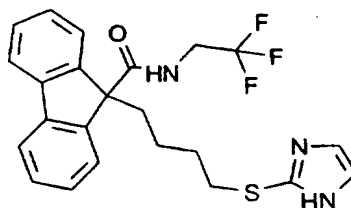
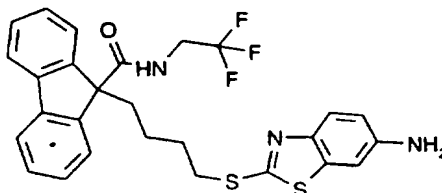
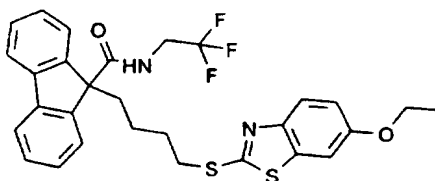
9-[2-[[[4-[(2-phenoxybenzoyl)amino]phenyl]-methyl]amino]ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

[1-[4-[9-[(2,2,2-trifluoroethyl)amino]-carbonyl]-9H-fluorene-9-yl]butyl]-1H-imidazol-4-yl]-carbamic acid;

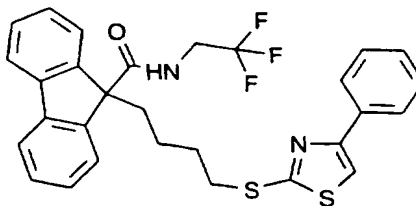
9-[4-[(4,5-diphenyl-1H-imidazol-2-yl)thio]-butyl]-N-[2-(4-methoxyphenyl)ethyl]-9H-fluorene-9-carboxamide;

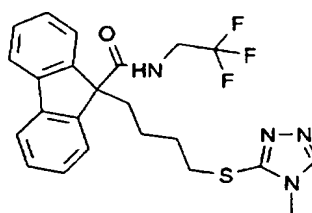
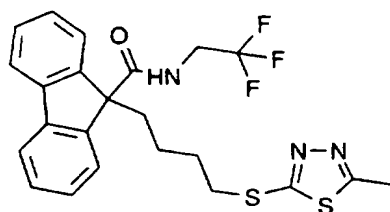
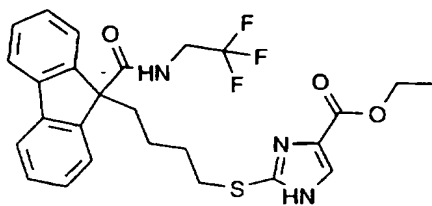
9-[4-[(6-ethoxy-2-benzothiazolyl)thio]-butyl]-N-propyl-9H-fluorene-9-carboxamide;

9-[4-(2-thiazolylthio)butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

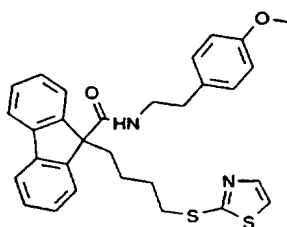
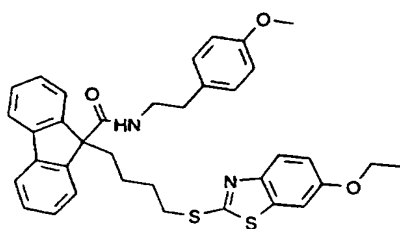


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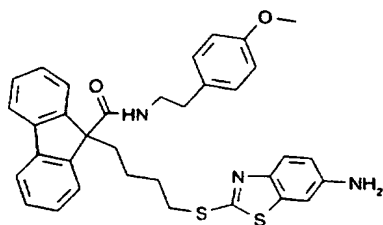


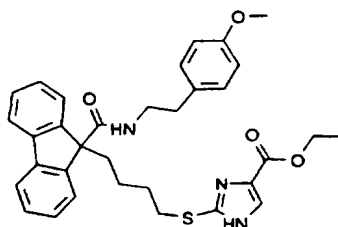
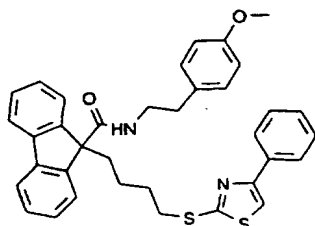
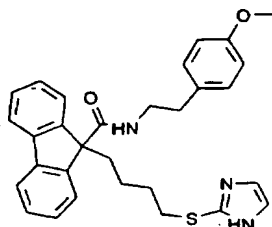


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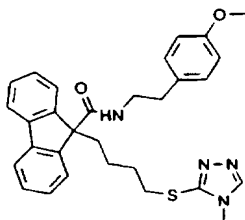
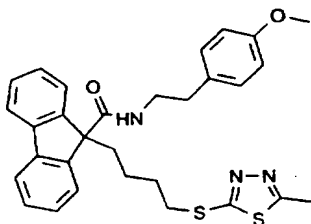


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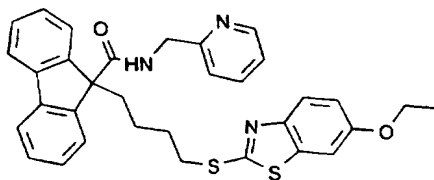


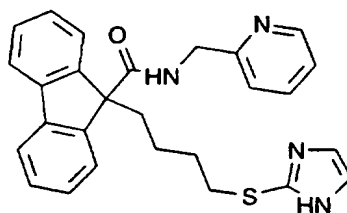
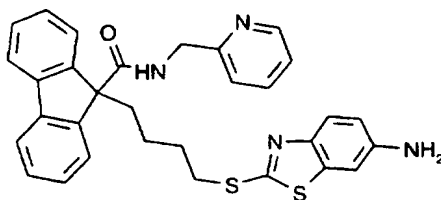
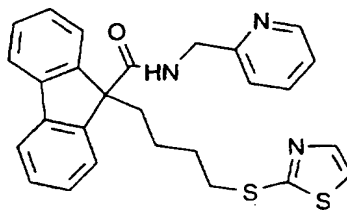


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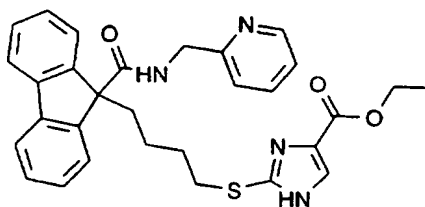
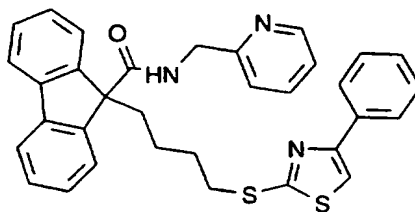


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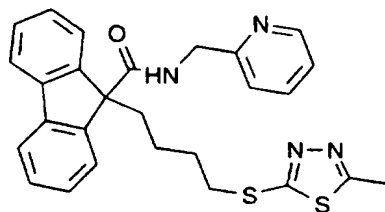


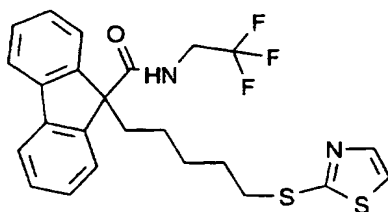
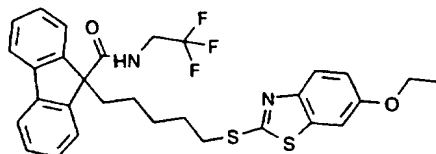
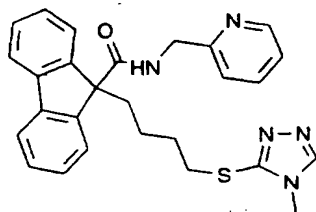


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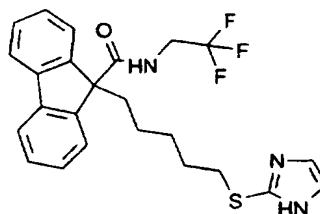
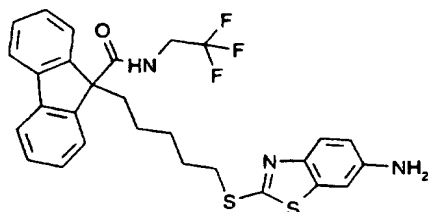


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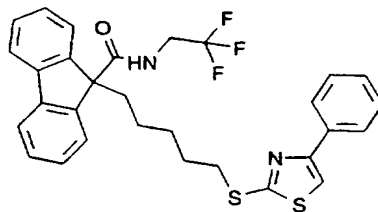


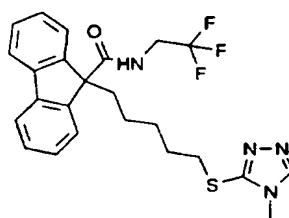
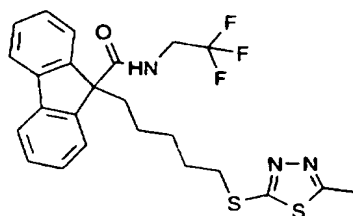
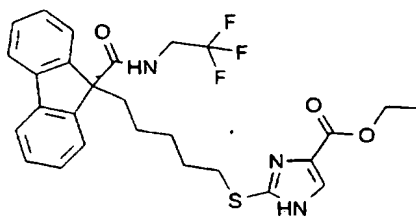


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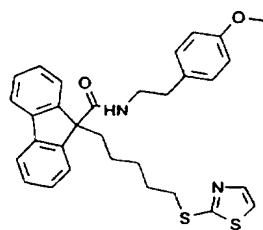
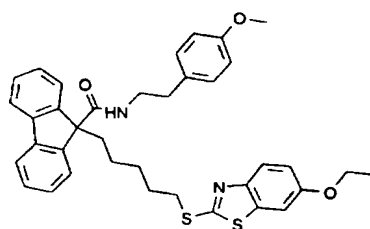


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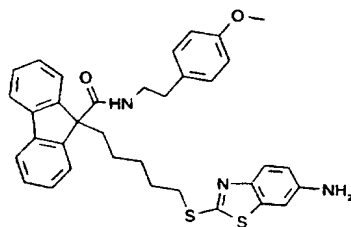


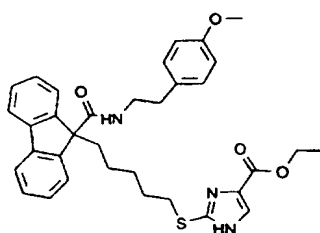
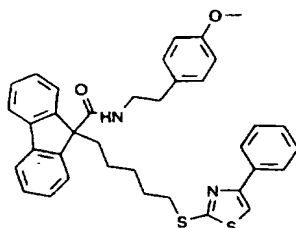
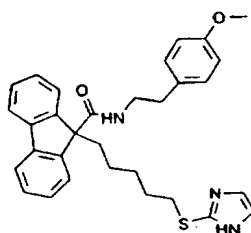


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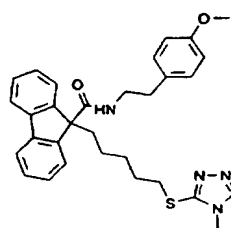
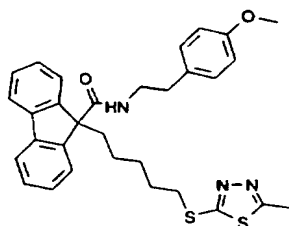


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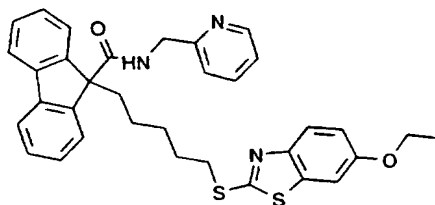


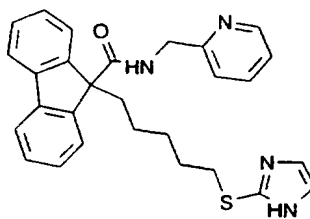
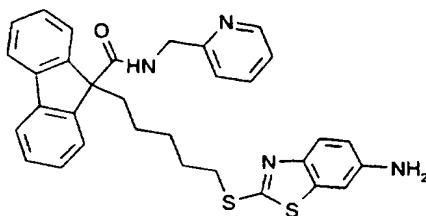
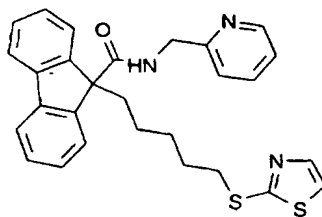


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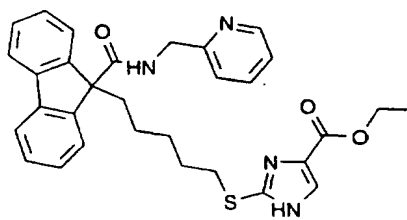
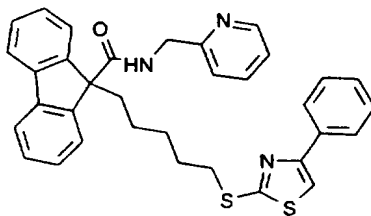


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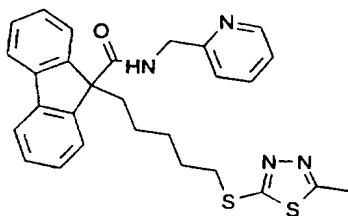


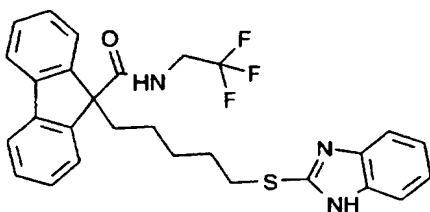
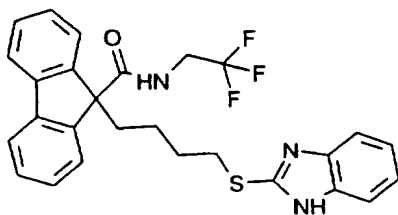
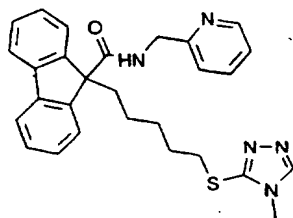


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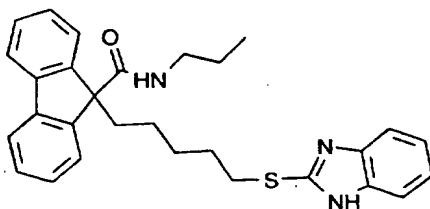
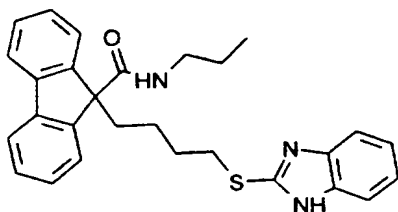


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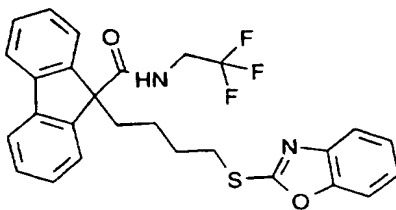


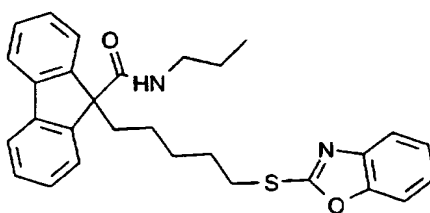
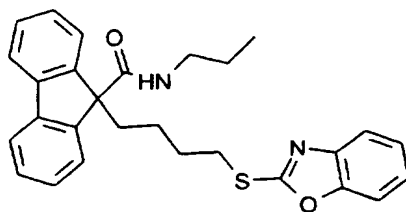
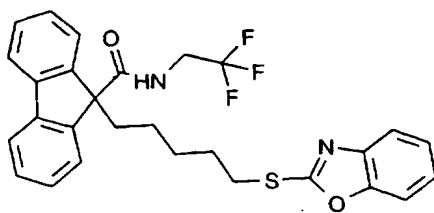


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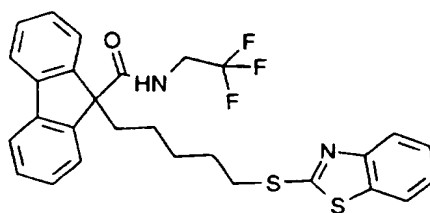
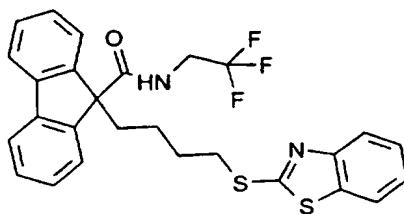


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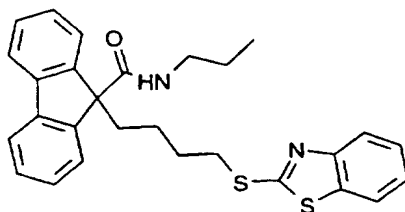


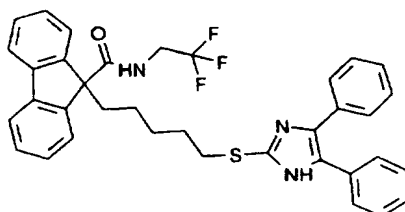
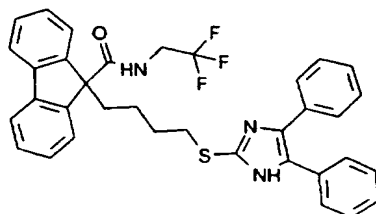
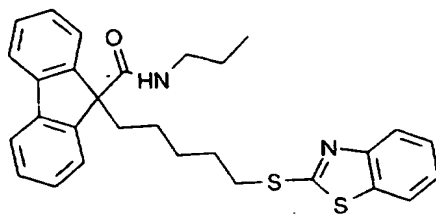


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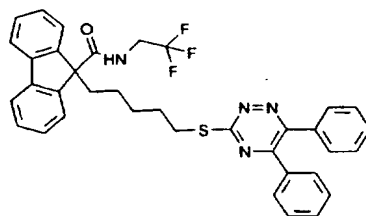
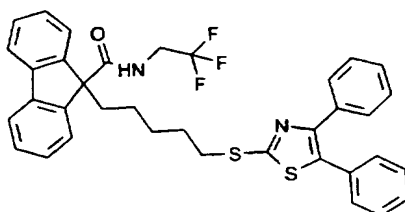


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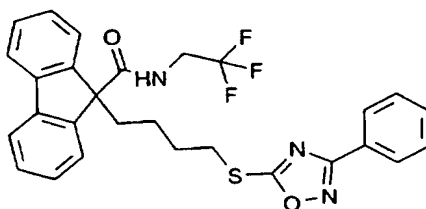


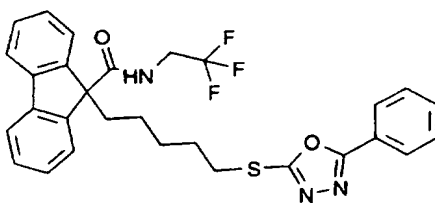
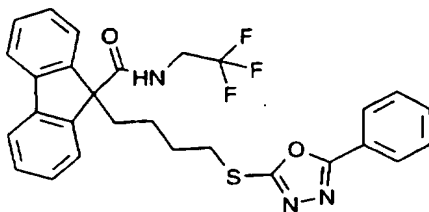
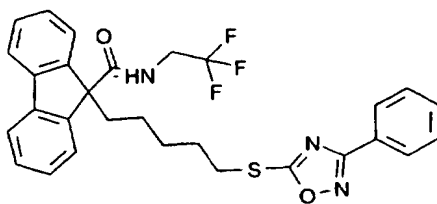


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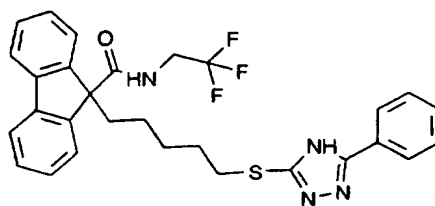
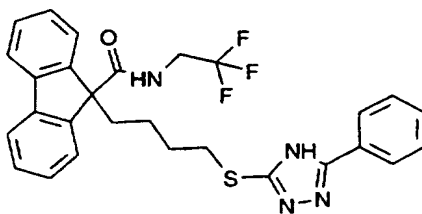


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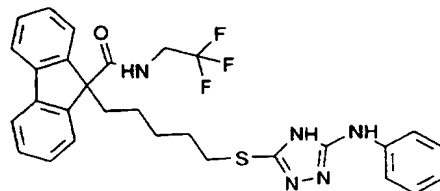


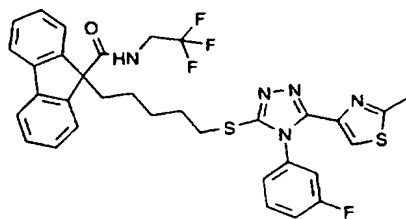
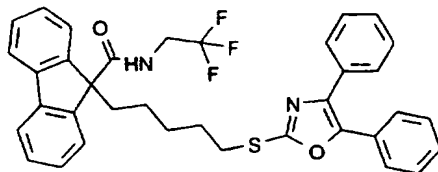
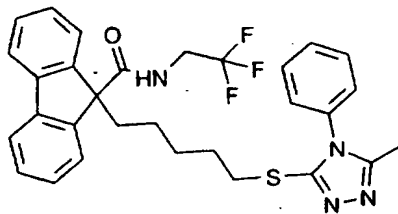


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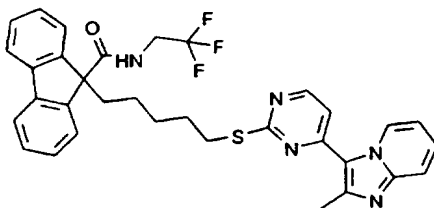
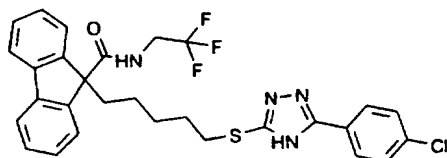


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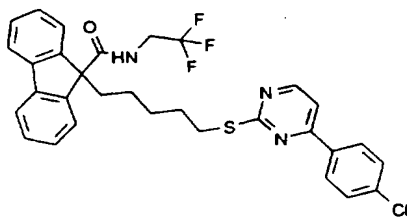


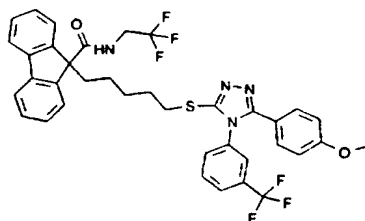
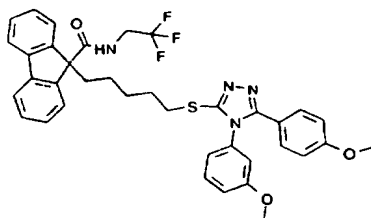
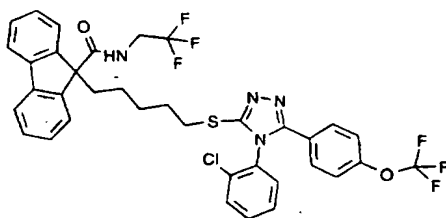


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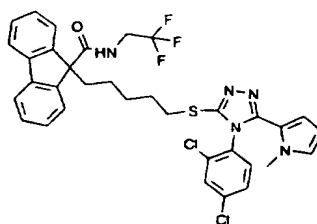
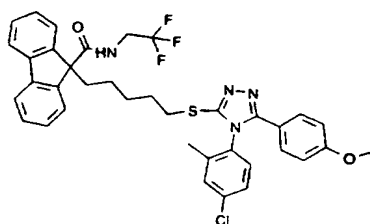


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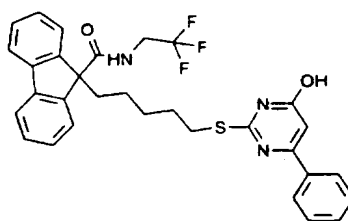


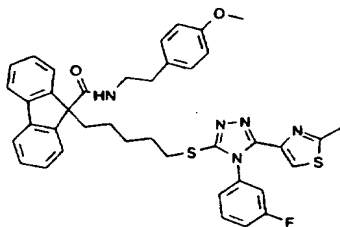
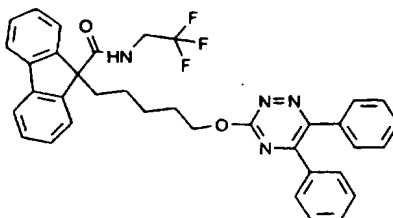
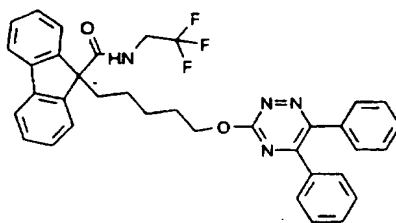


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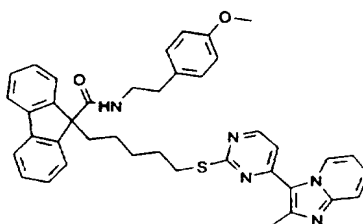
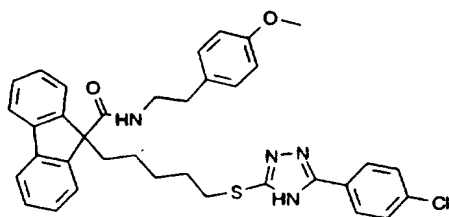


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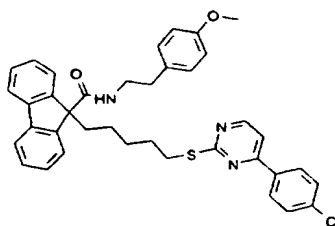


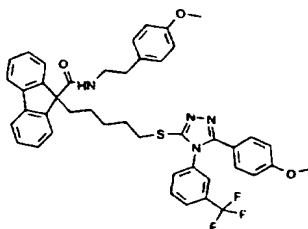
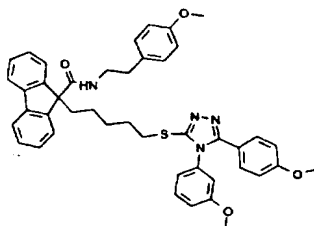
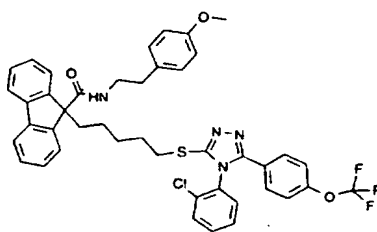


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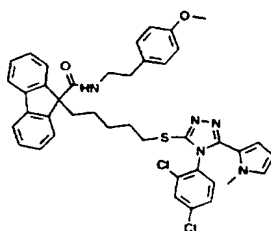
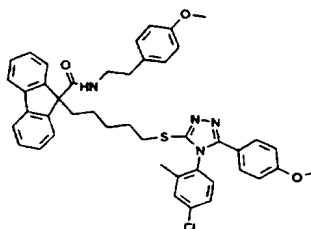


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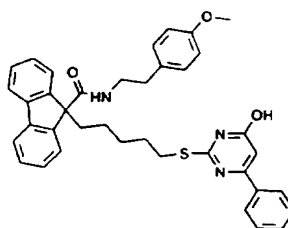


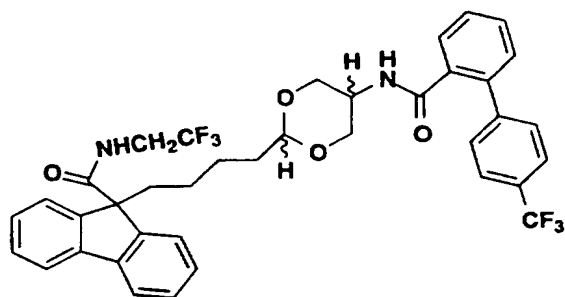
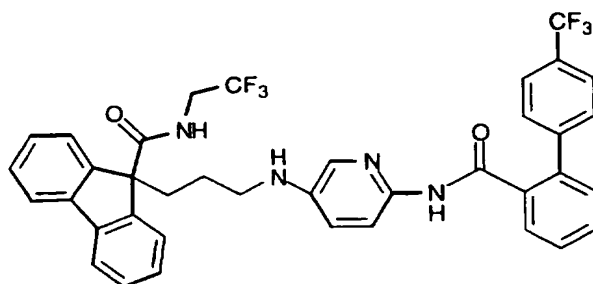
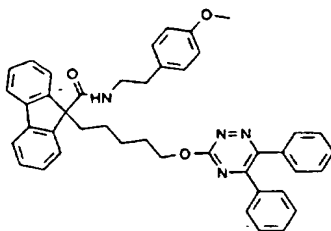


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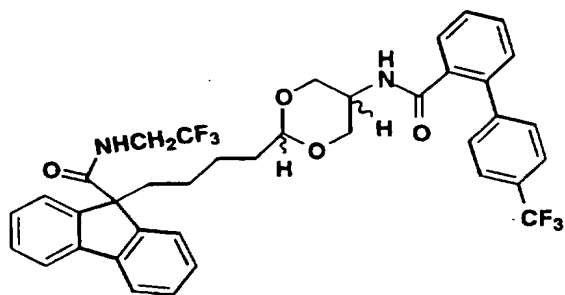


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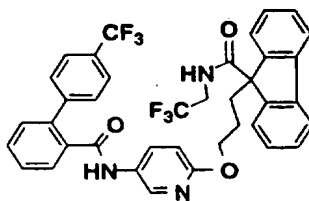


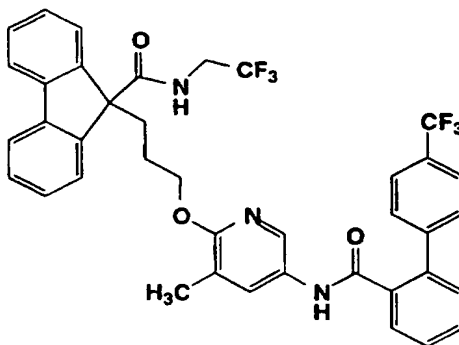
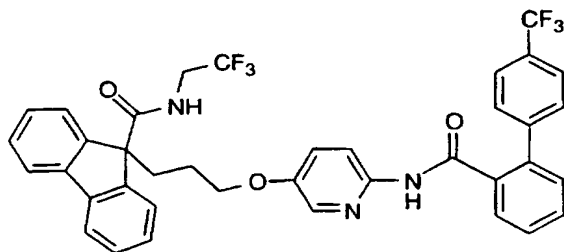
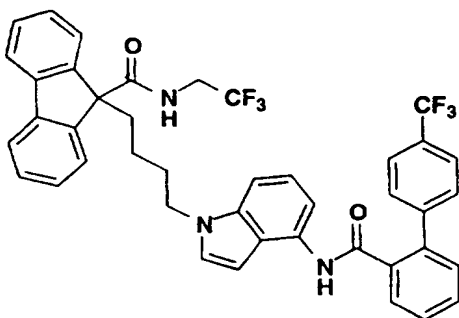


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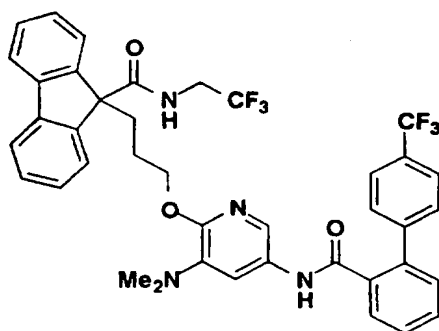


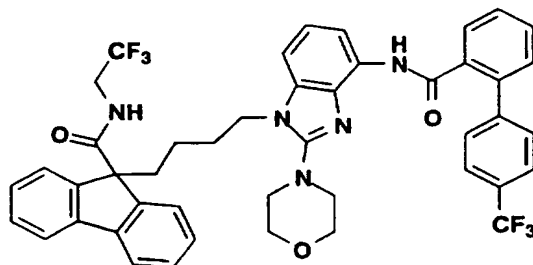
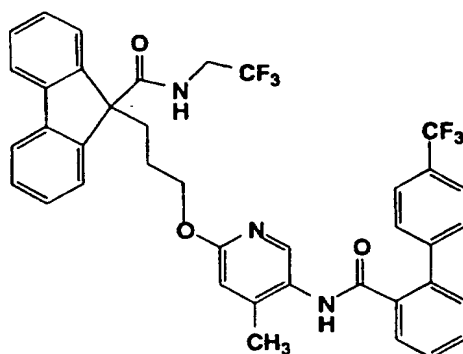
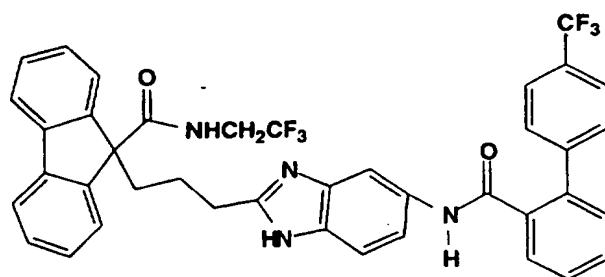
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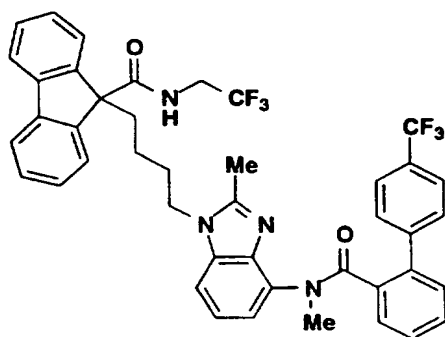


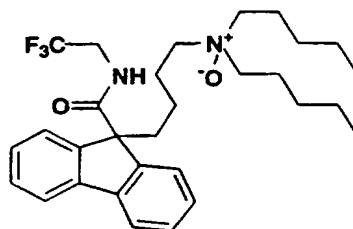
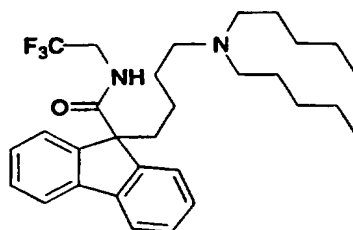
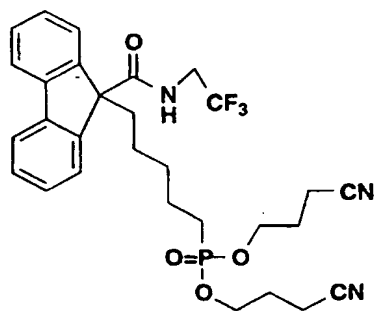
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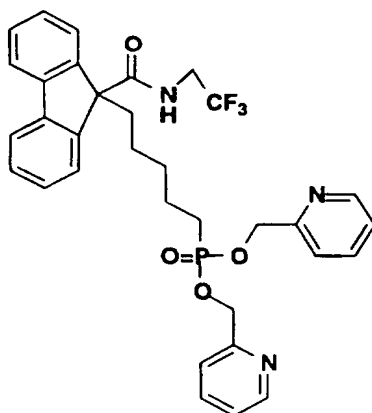
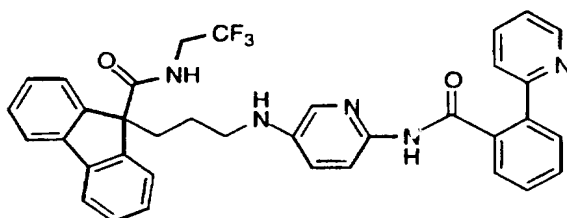


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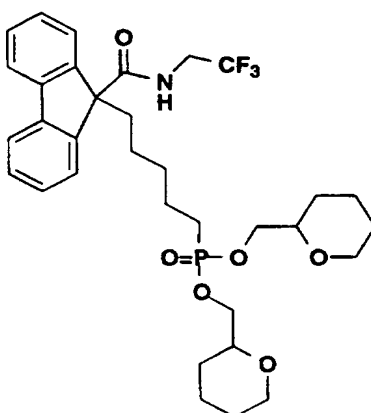
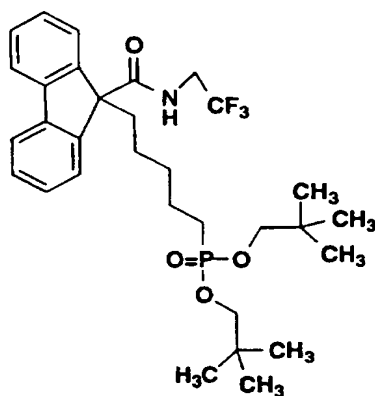
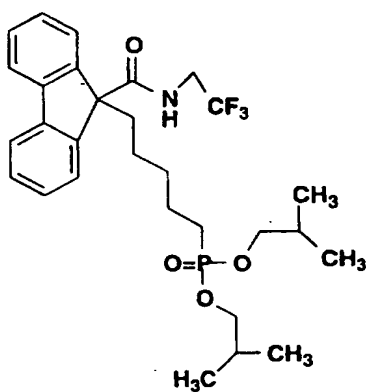




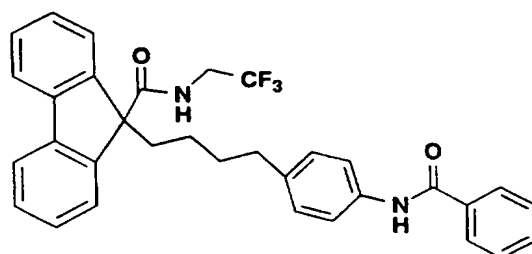
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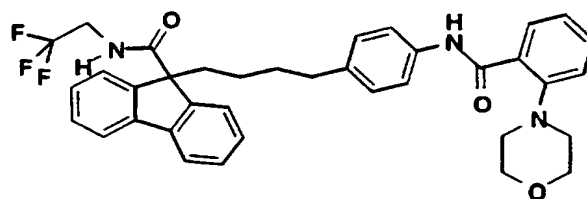
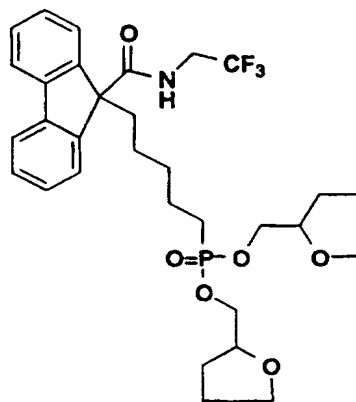
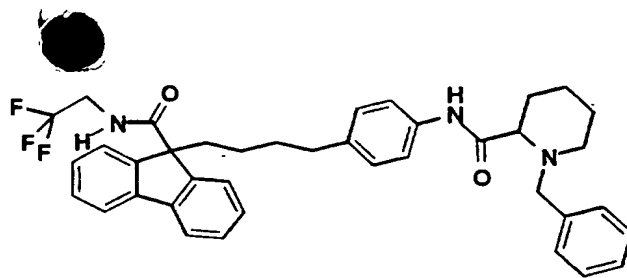


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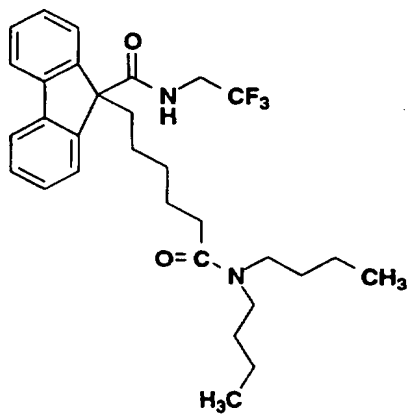


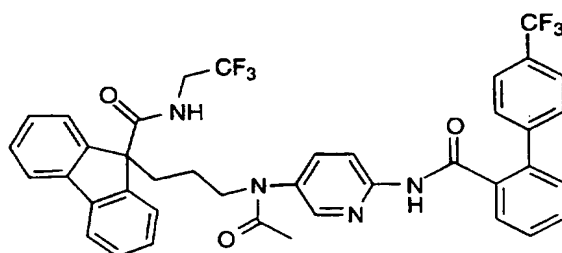
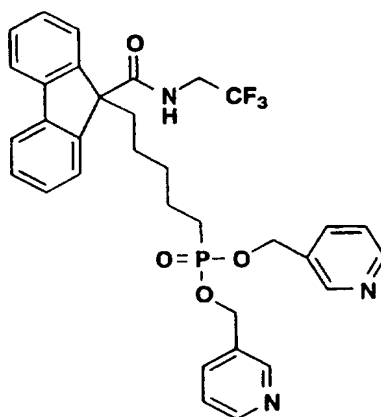
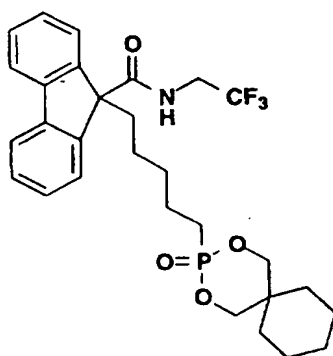
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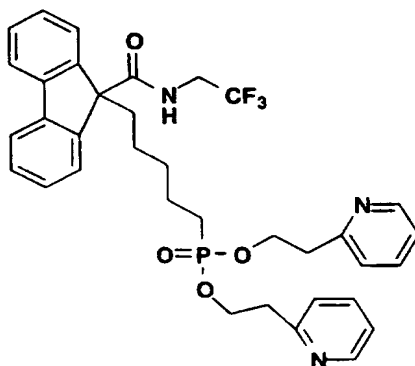


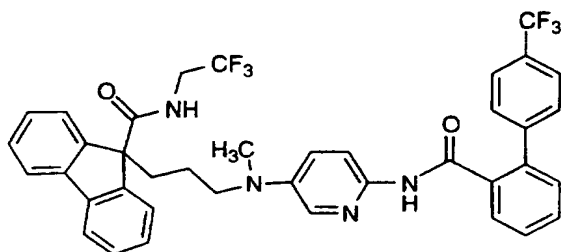
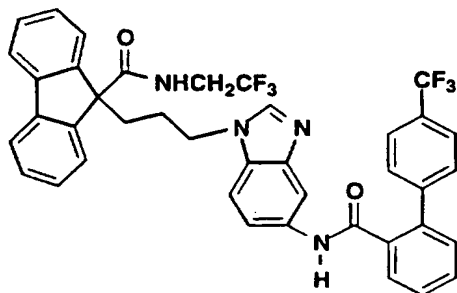
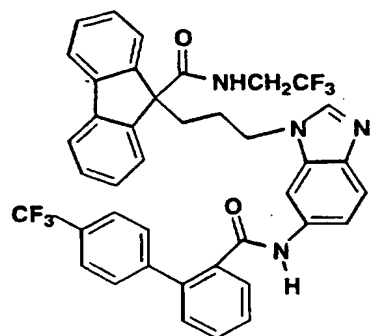
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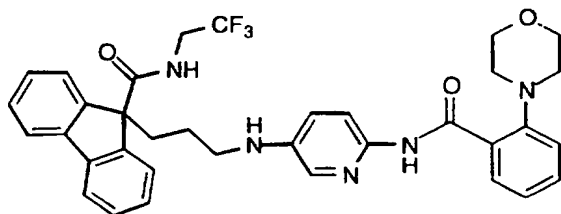


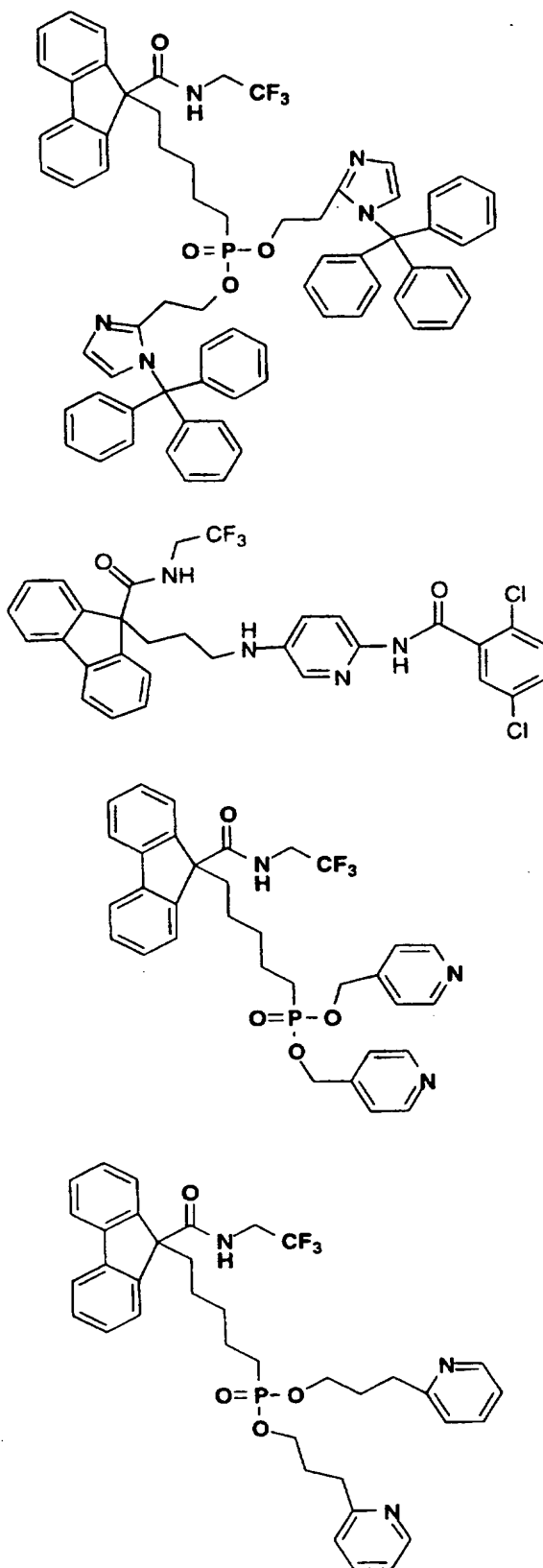
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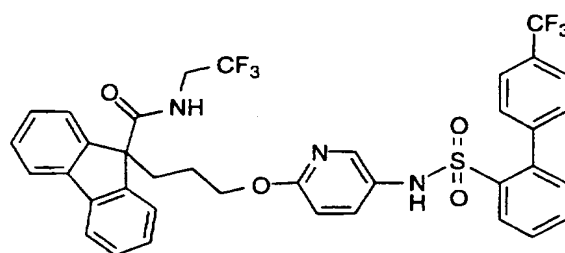
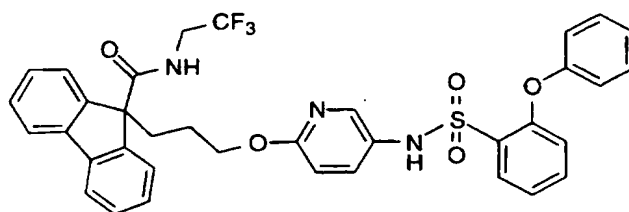
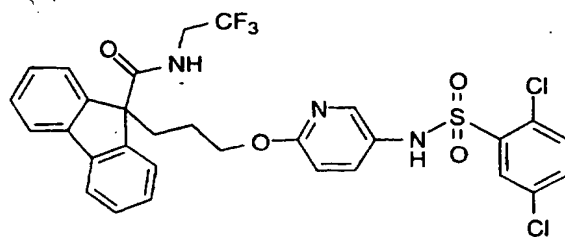


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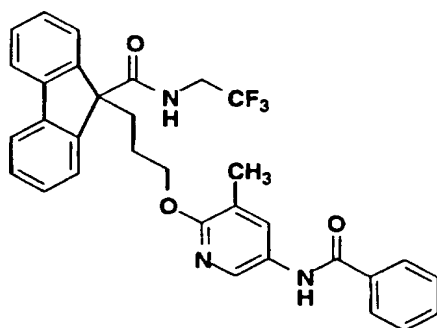
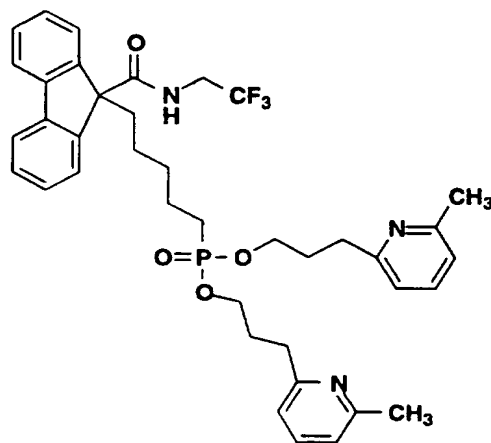




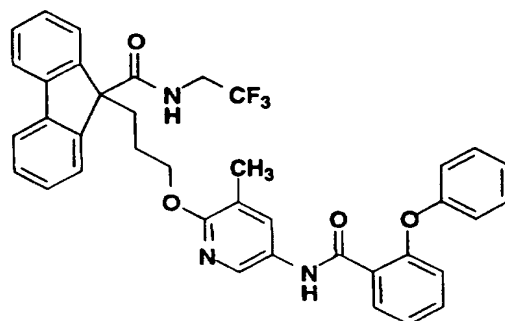
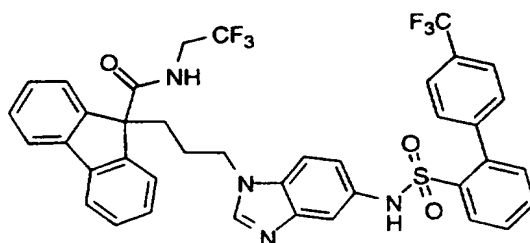
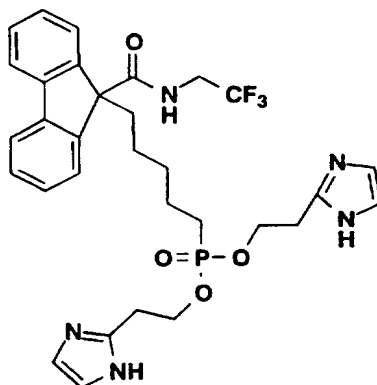
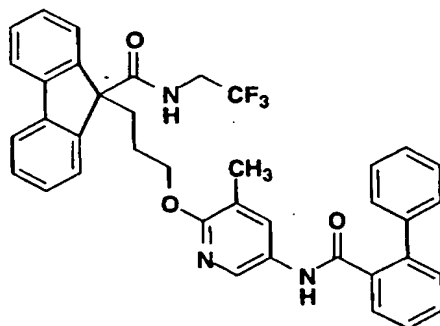
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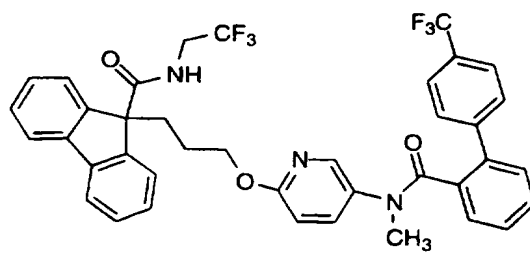
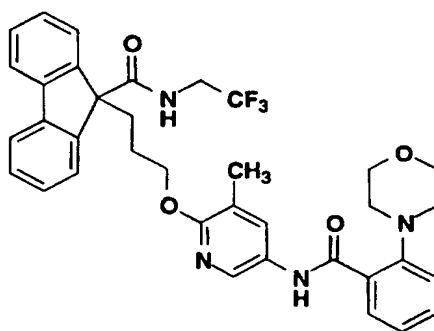
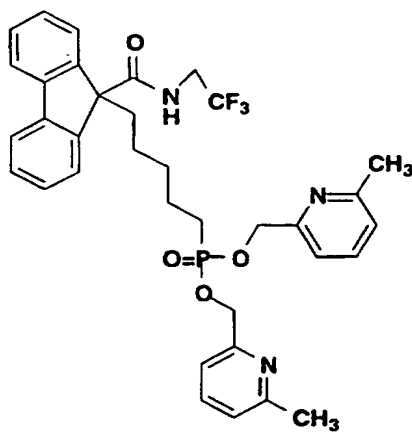
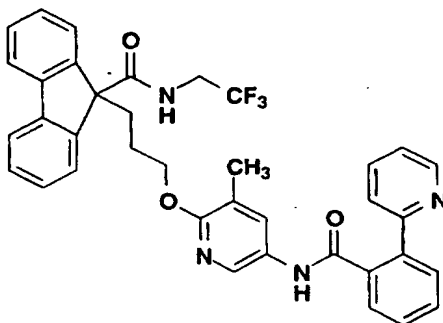
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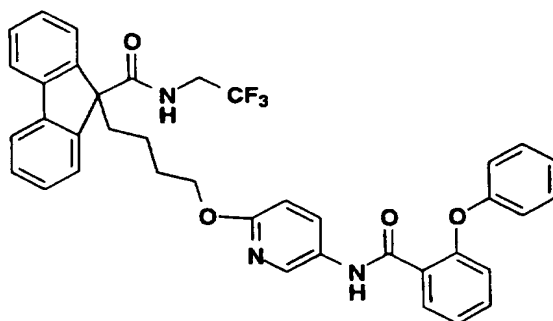
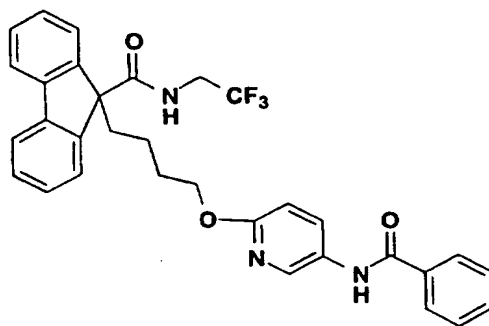
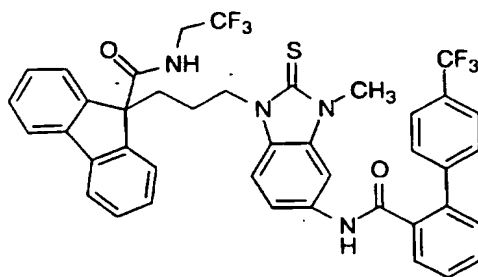


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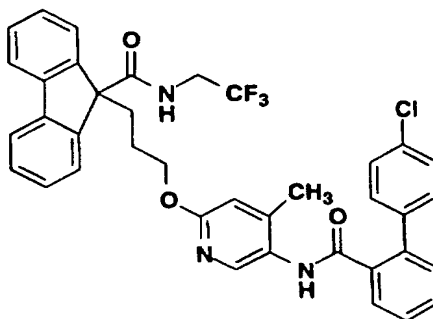


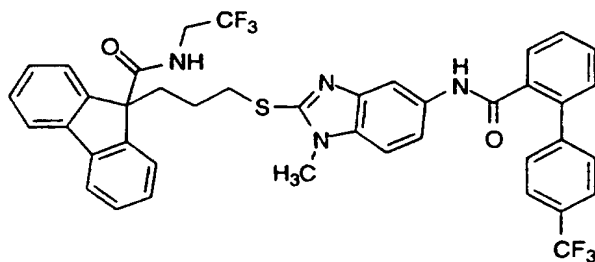
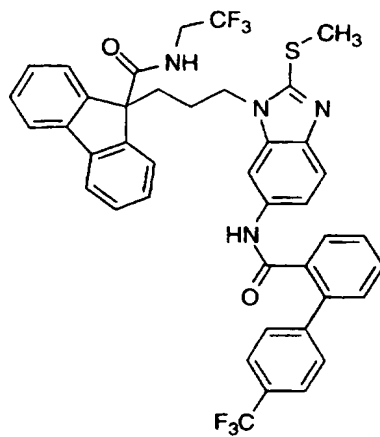
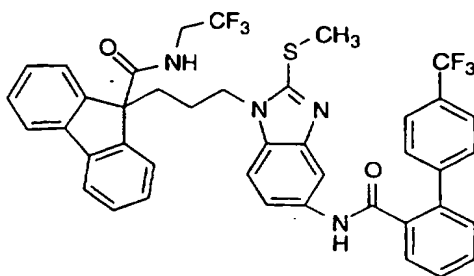
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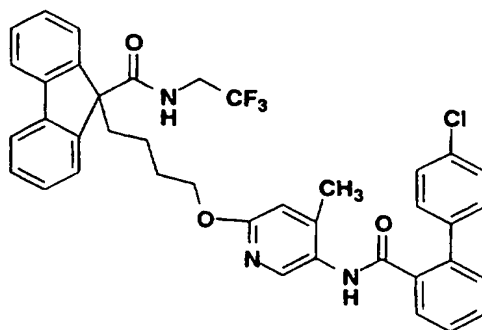
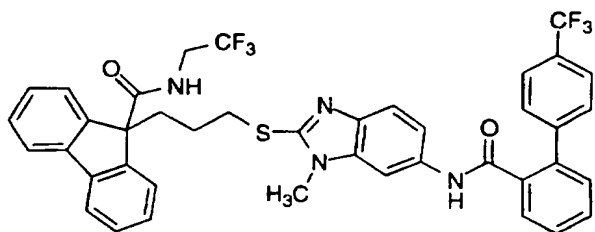


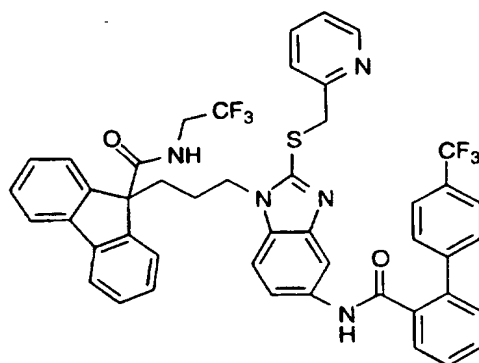
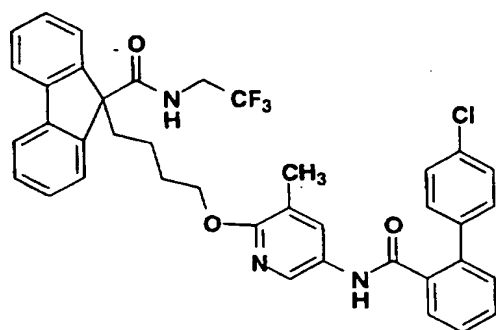
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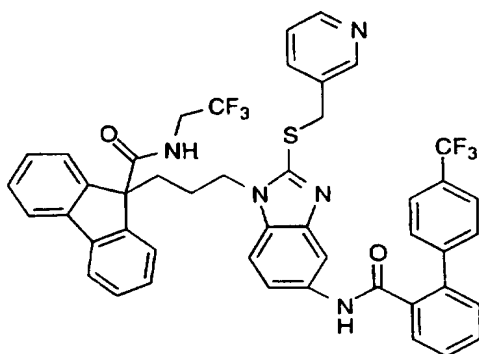
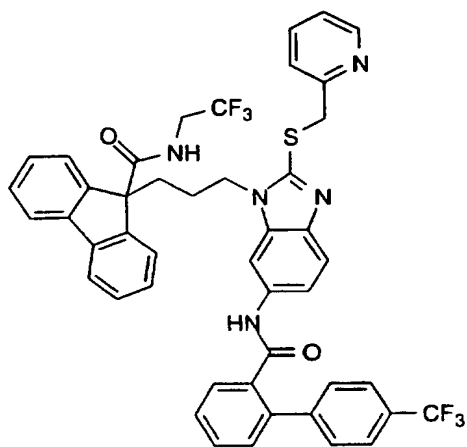


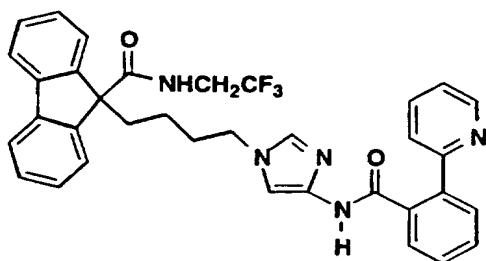
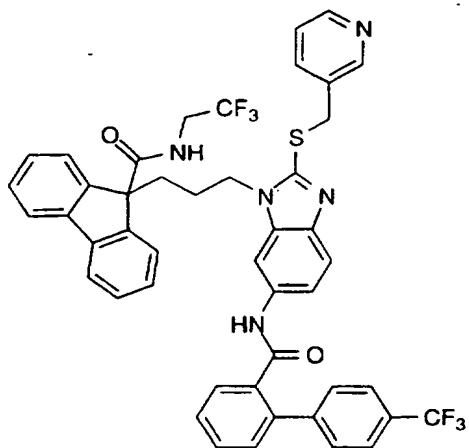
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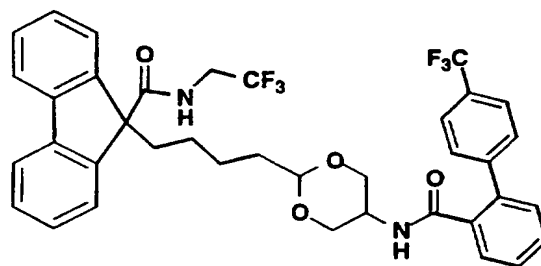


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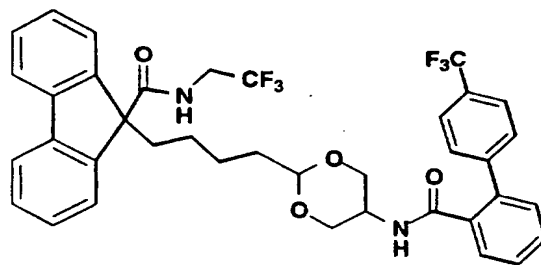




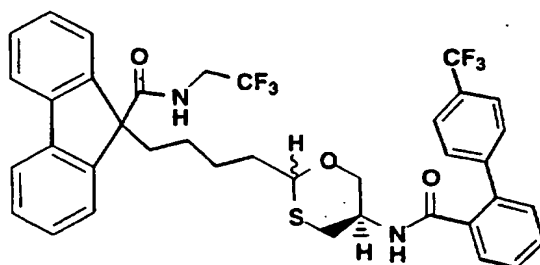
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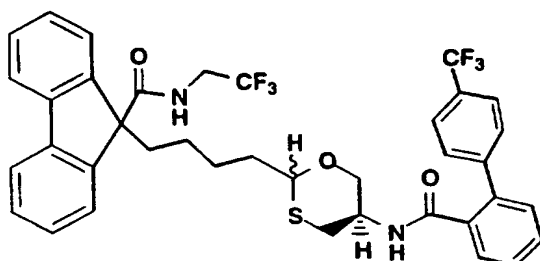
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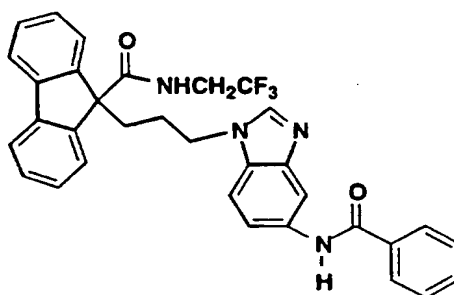
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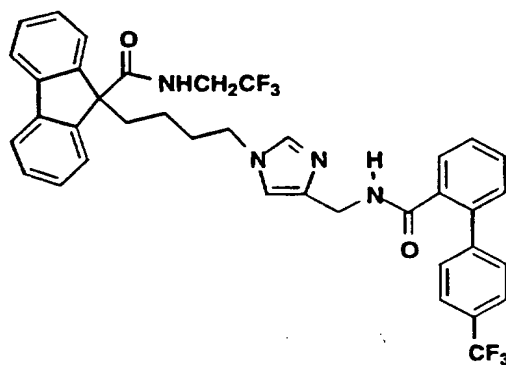
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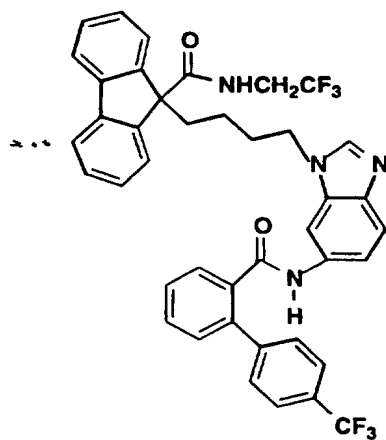
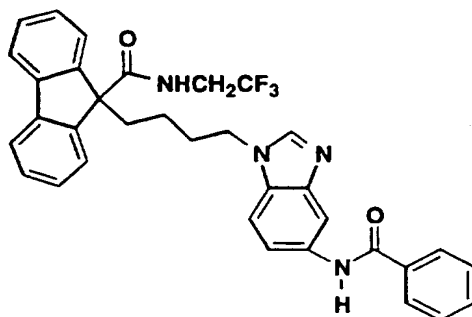
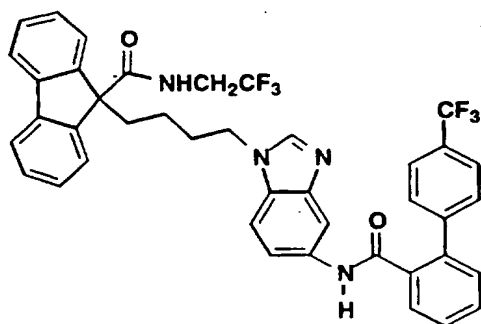


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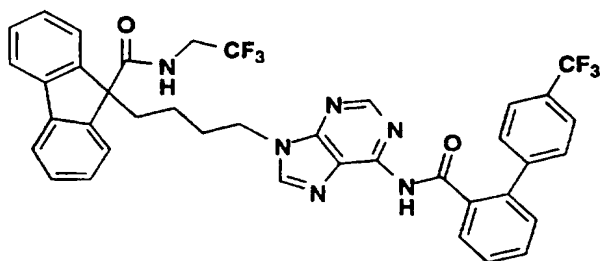


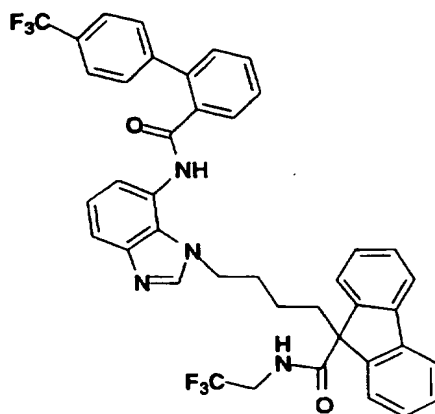
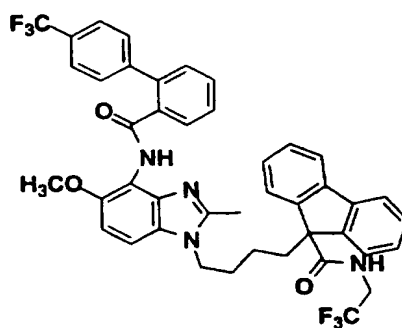
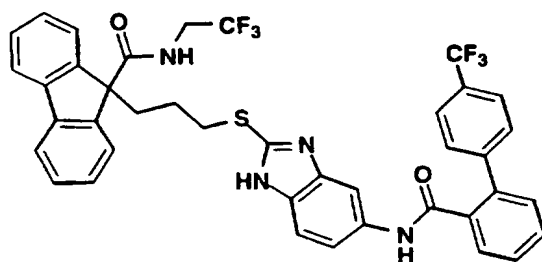
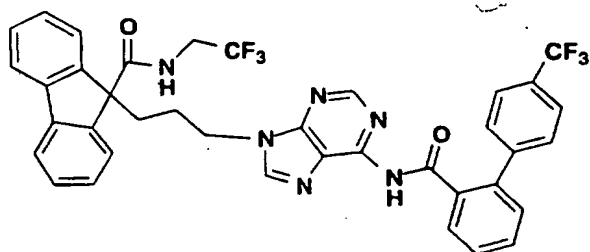
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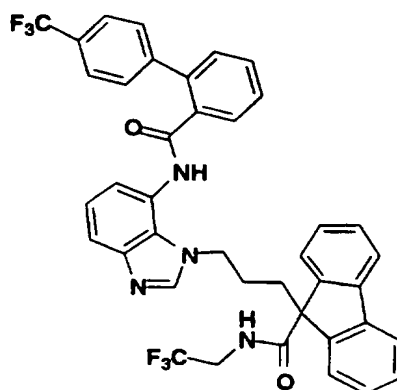
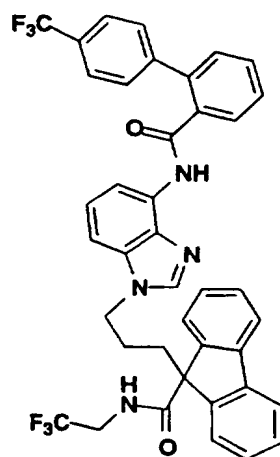
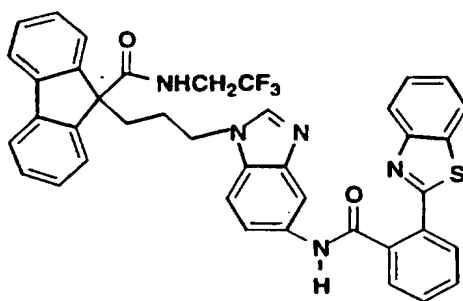




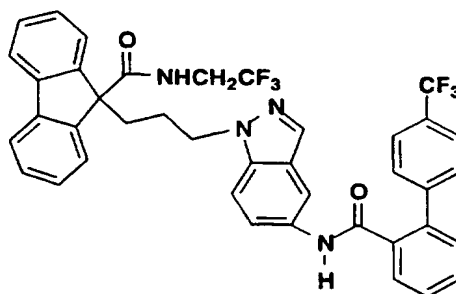
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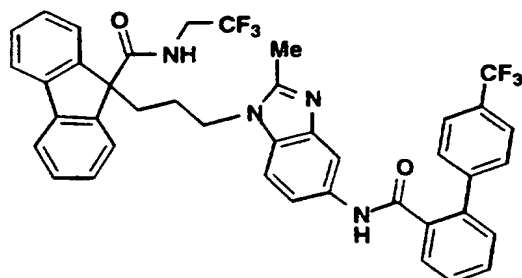
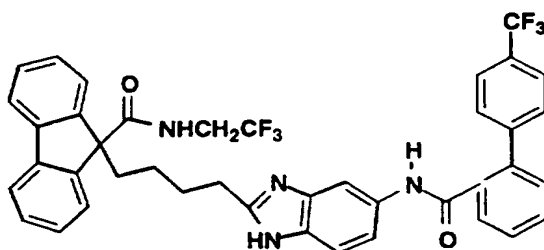
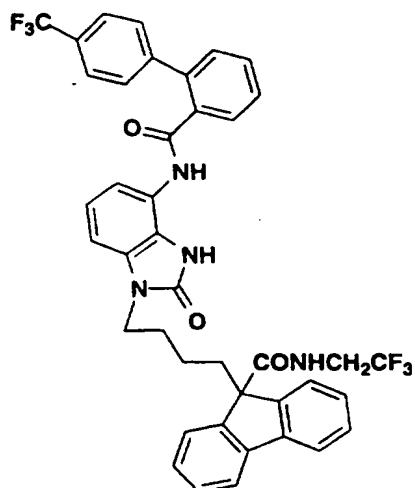




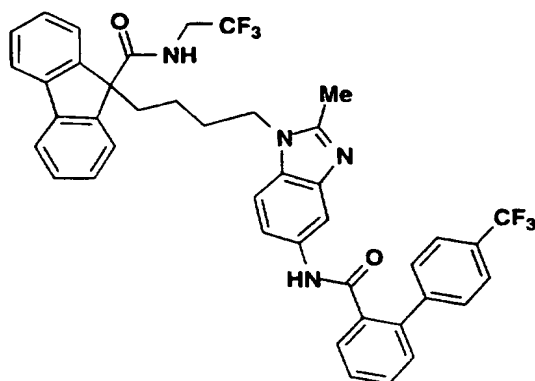


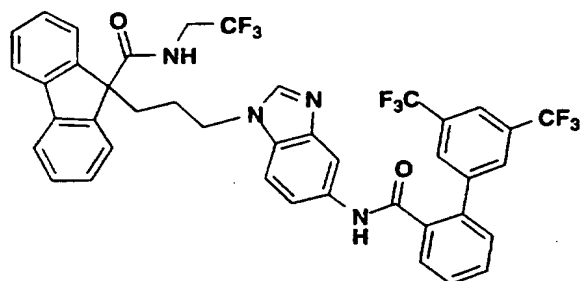
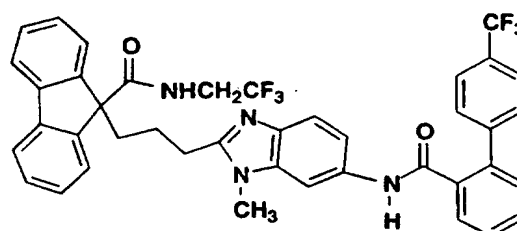
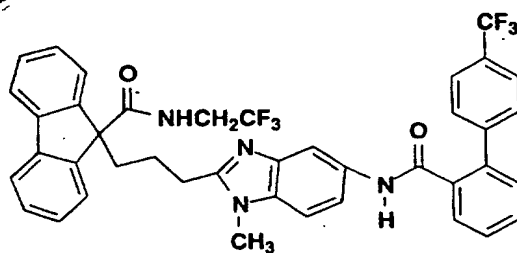
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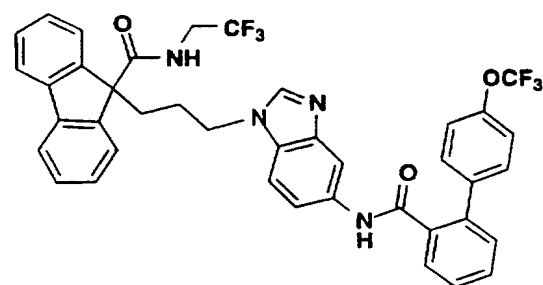
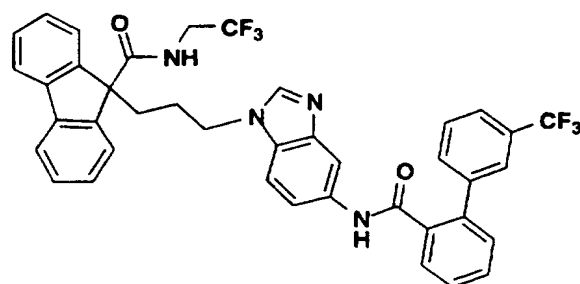


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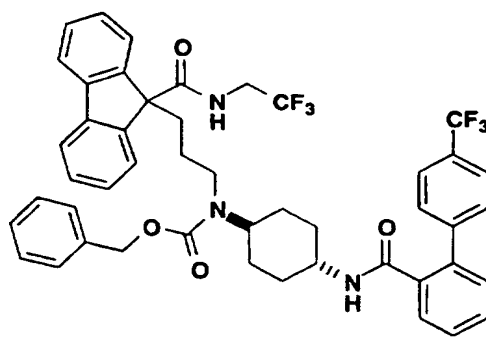
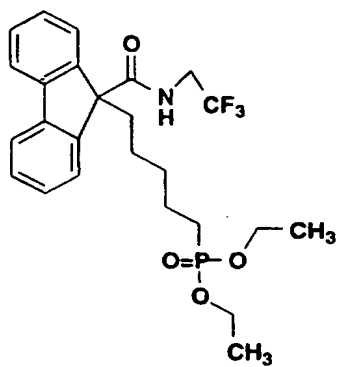




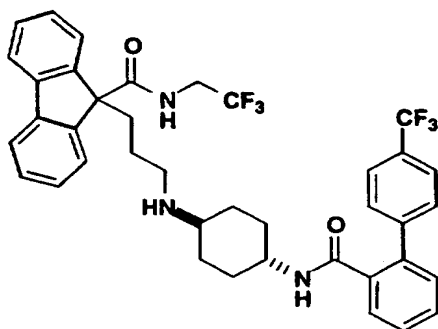
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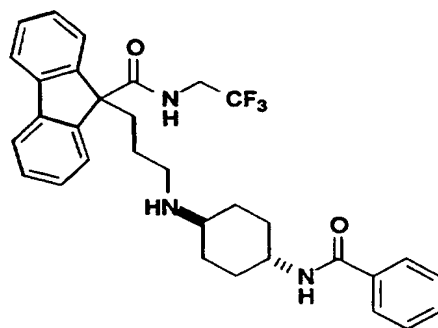


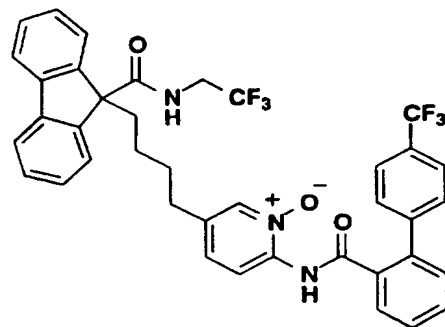
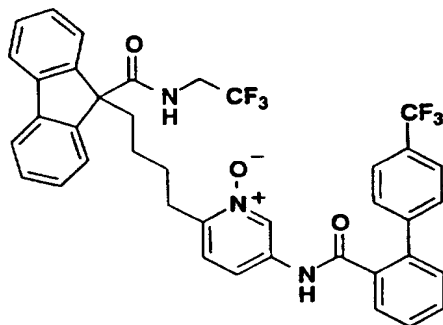
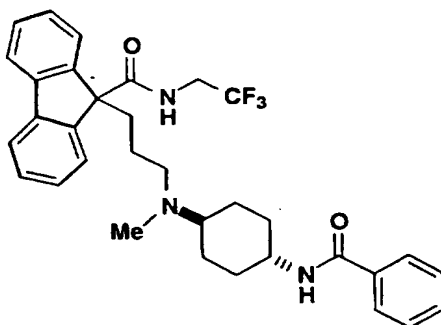
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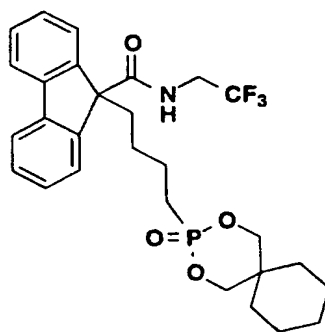
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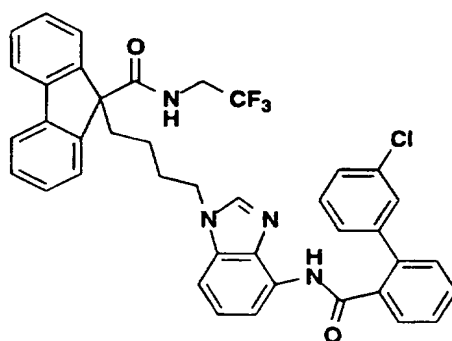
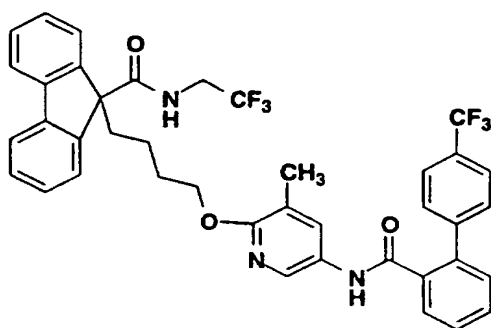
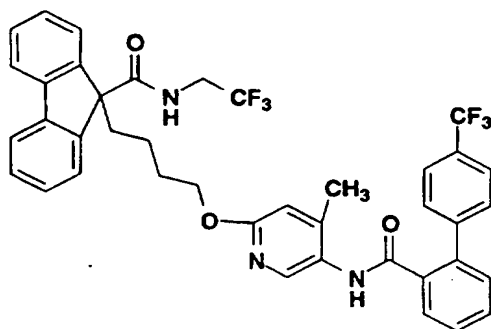
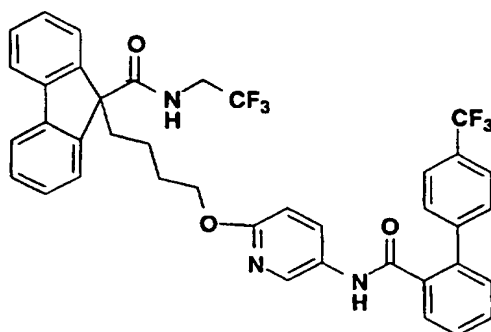
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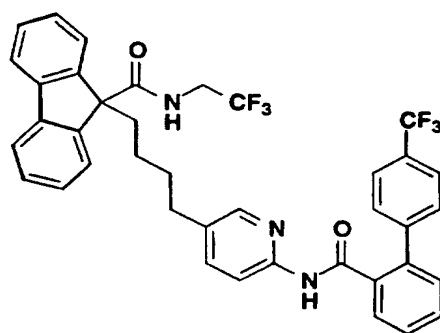
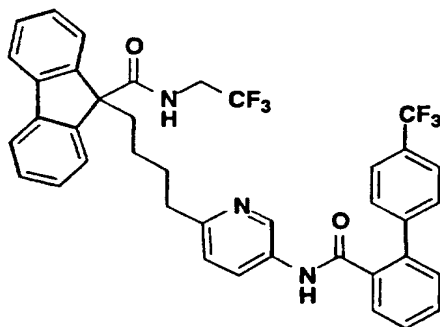
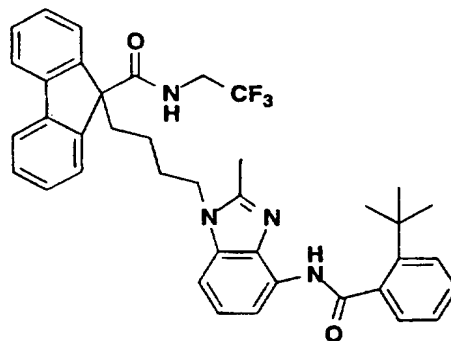
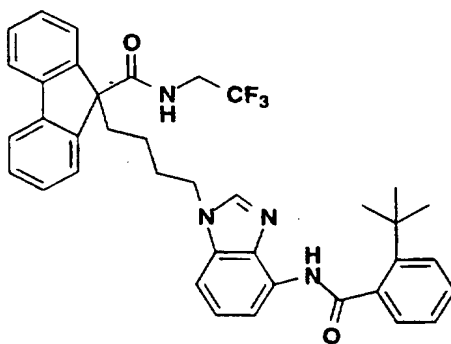


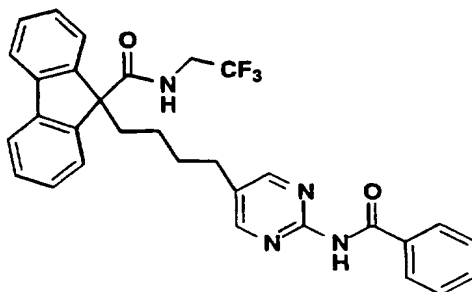
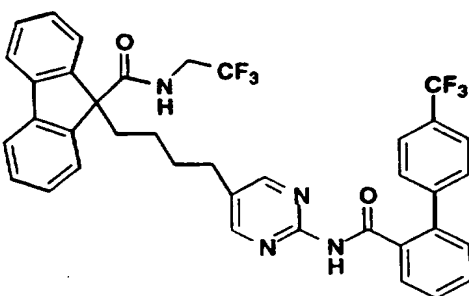
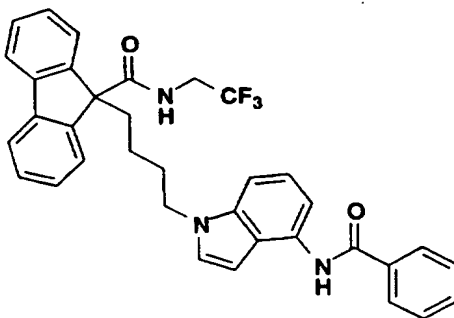
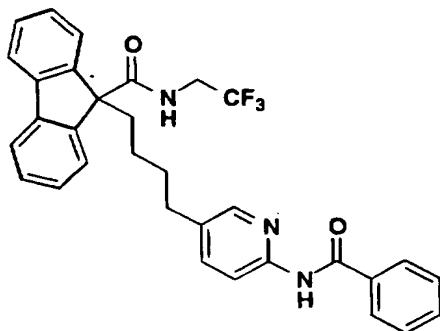
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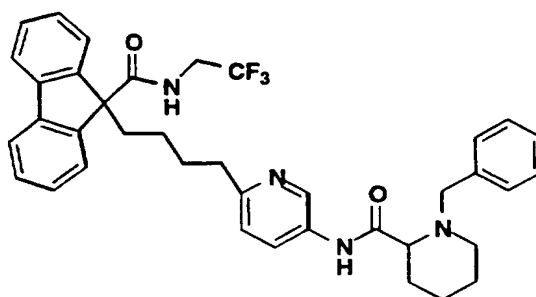
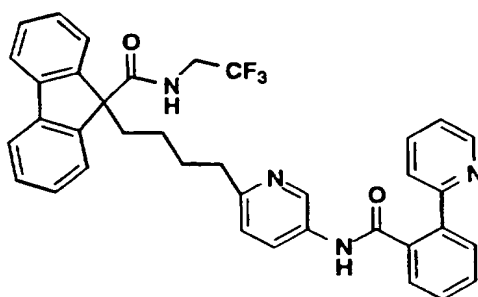
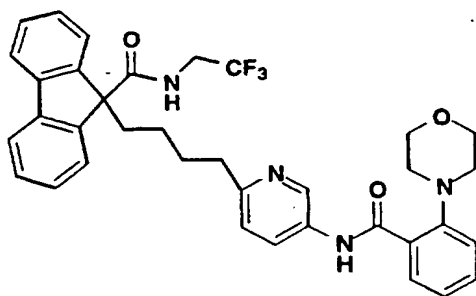




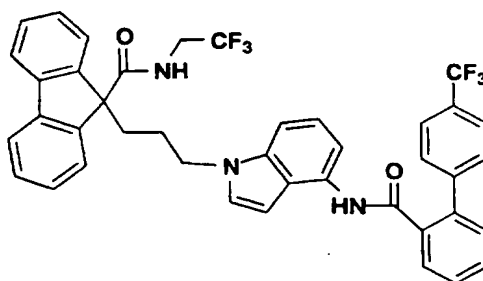
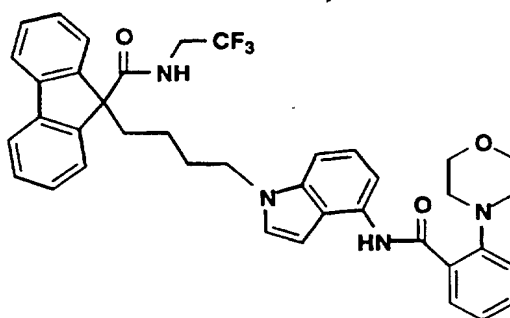
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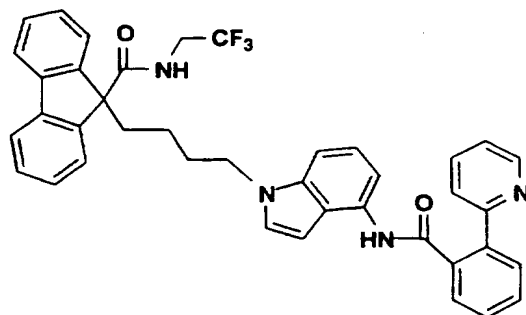
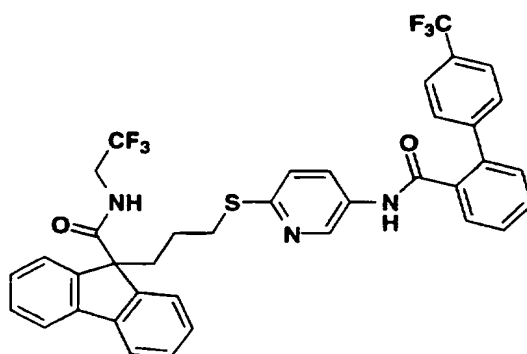
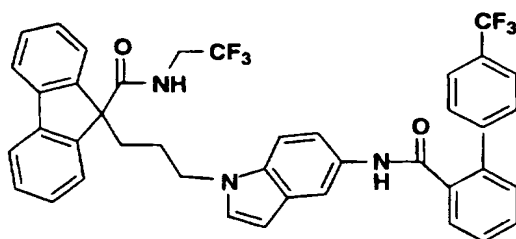
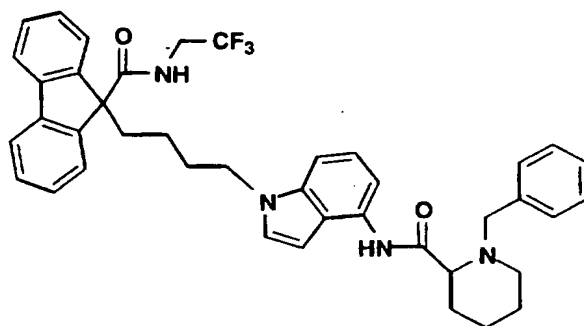




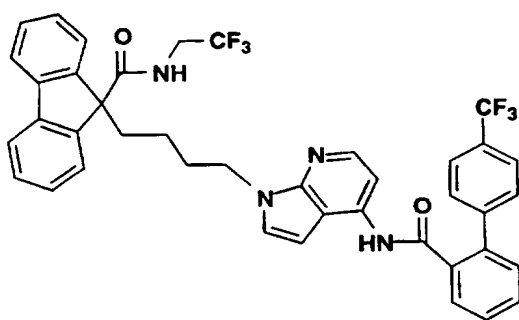
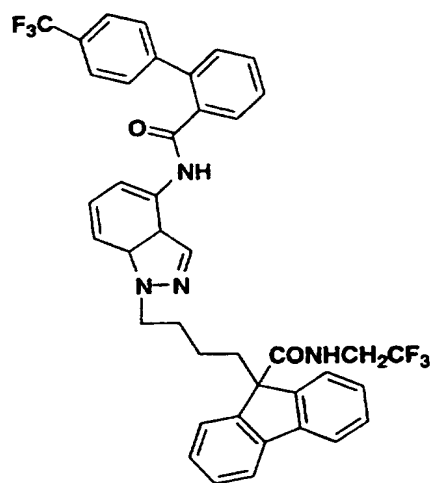
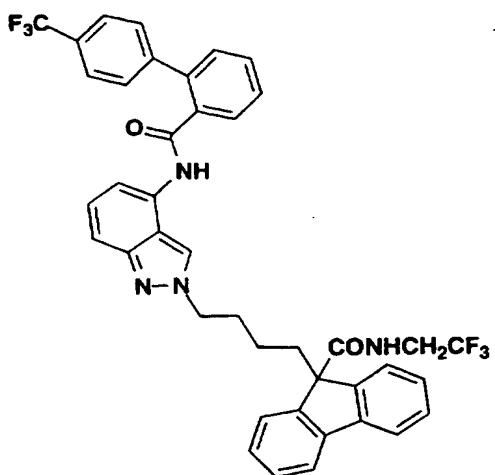


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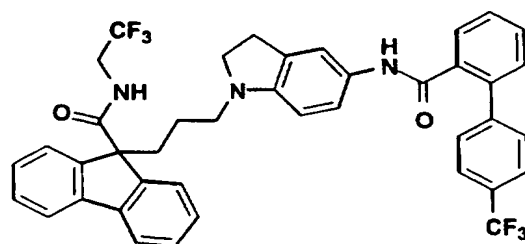


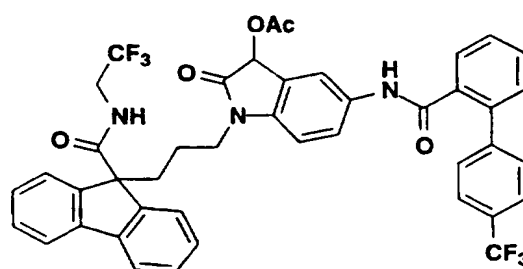
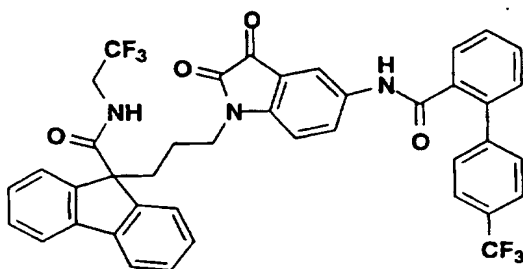


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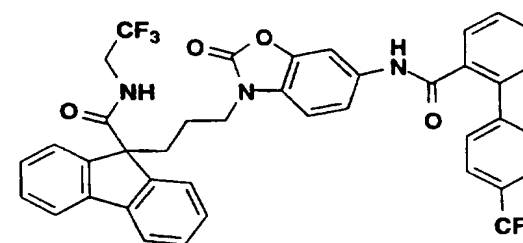
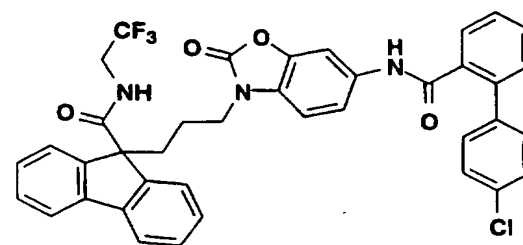
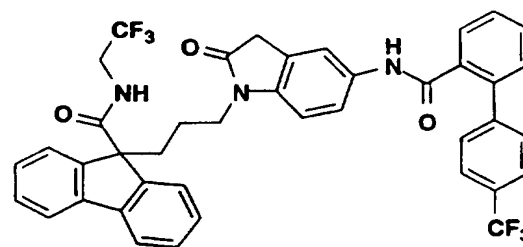


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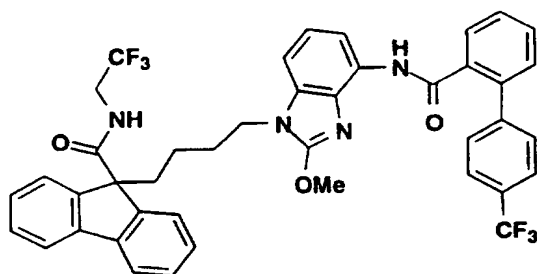
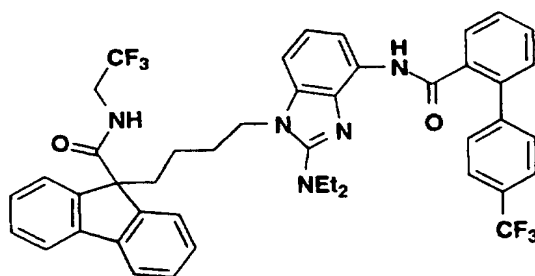
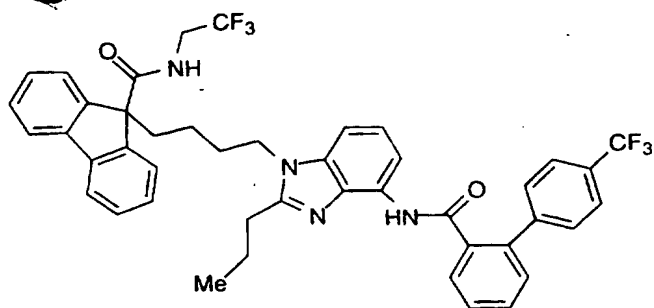




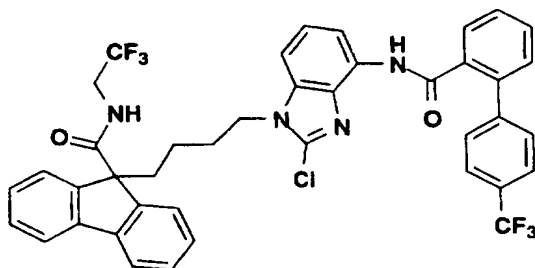
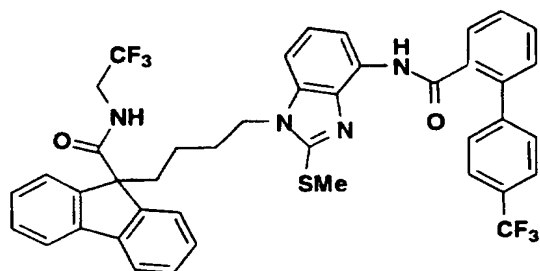
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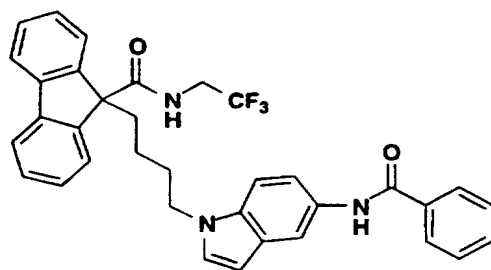
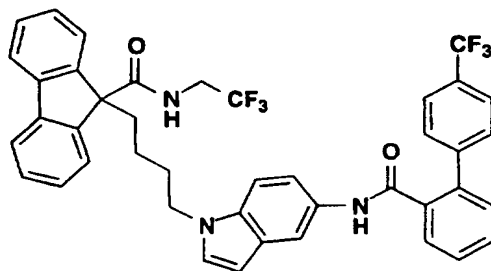
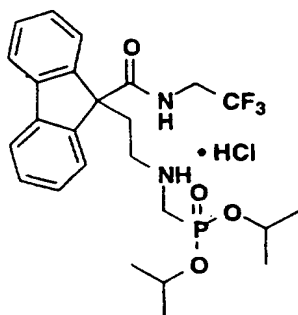
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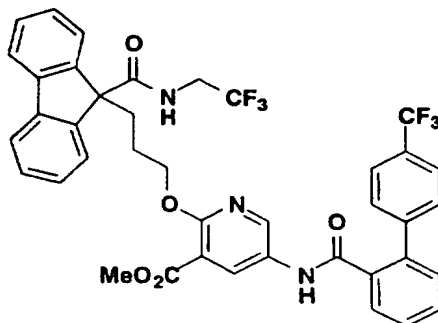
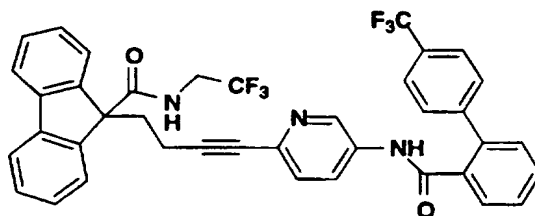
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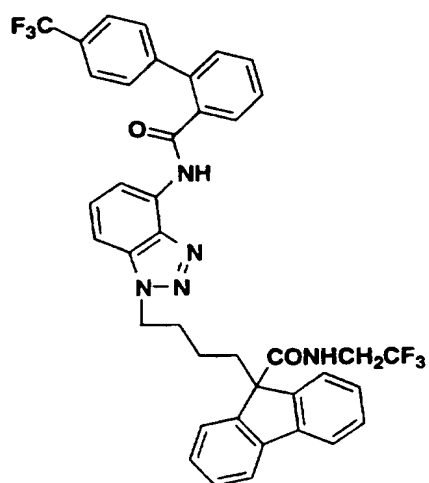
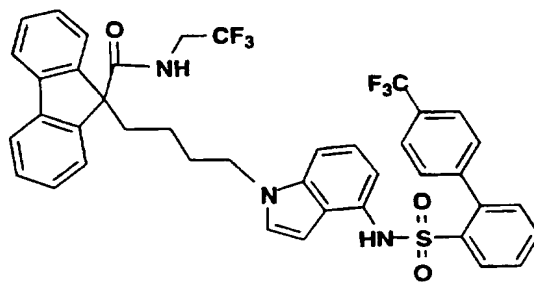
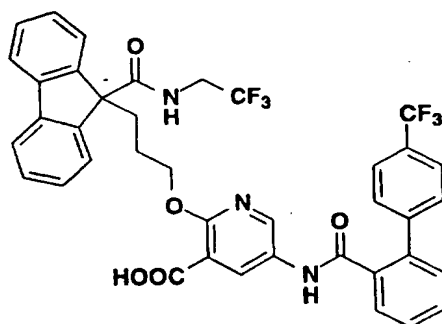
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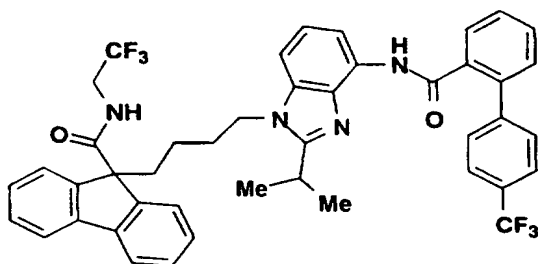
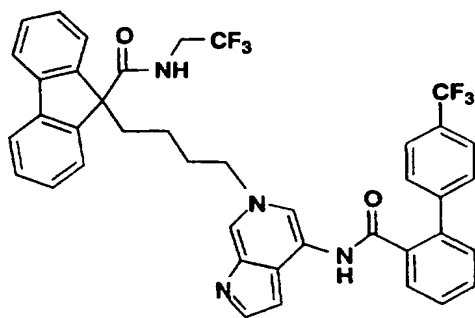
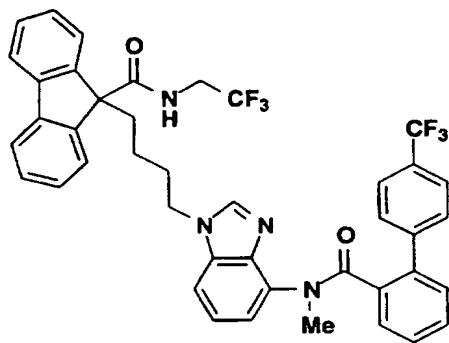
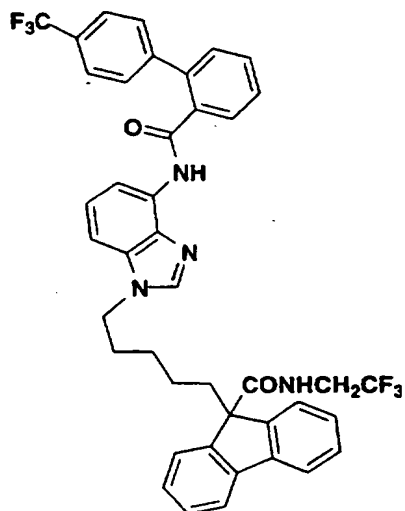


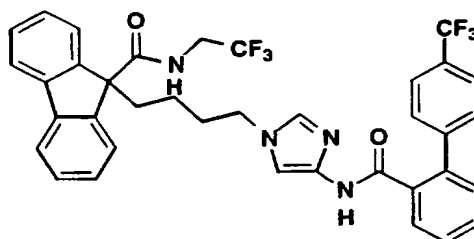
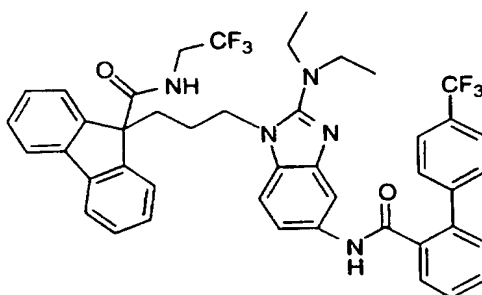
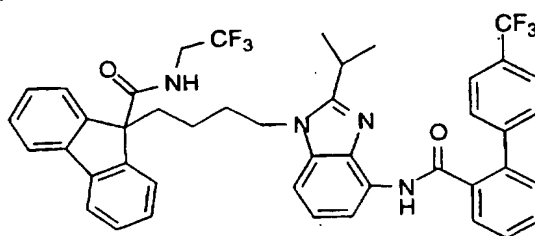
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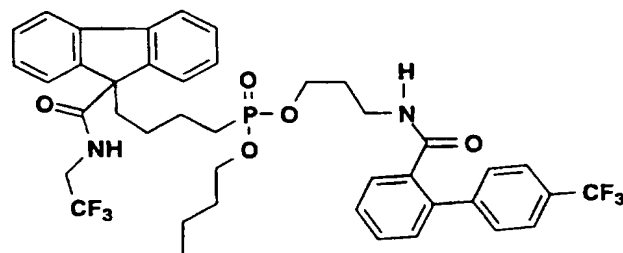
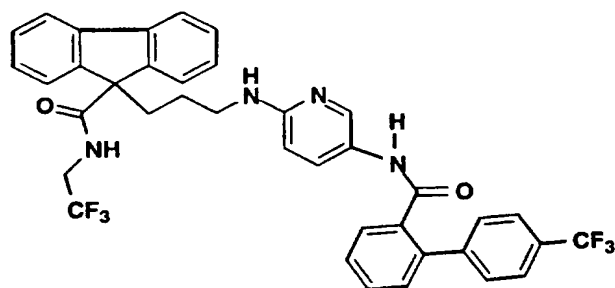
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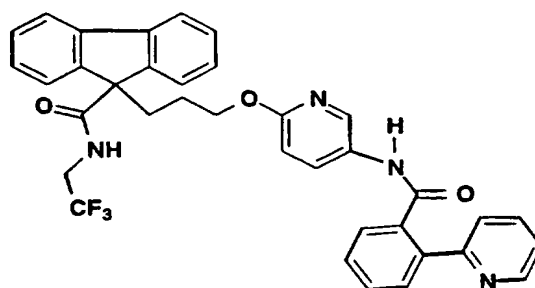
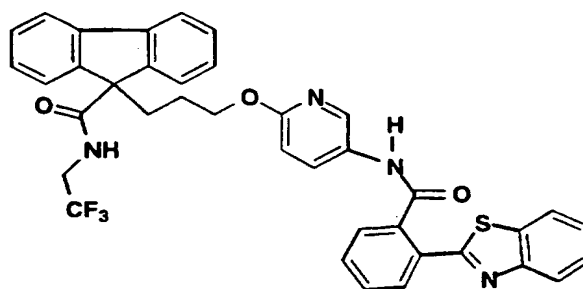
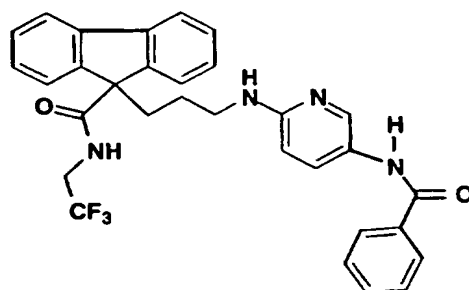
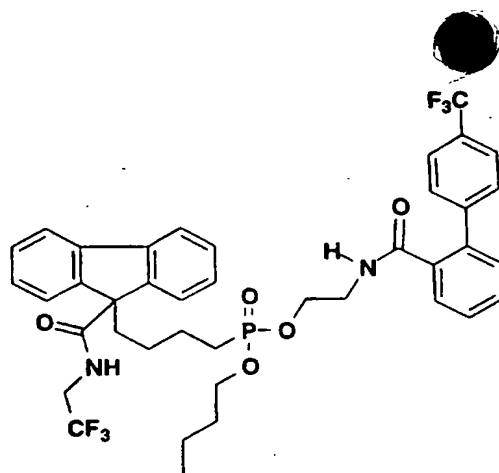




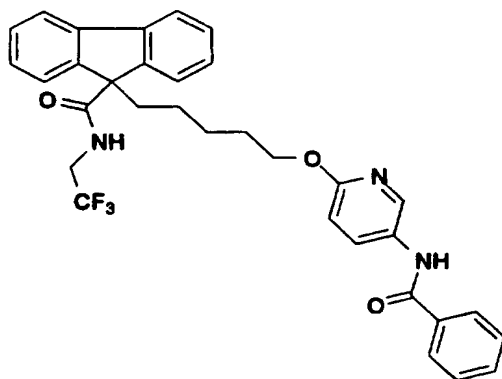
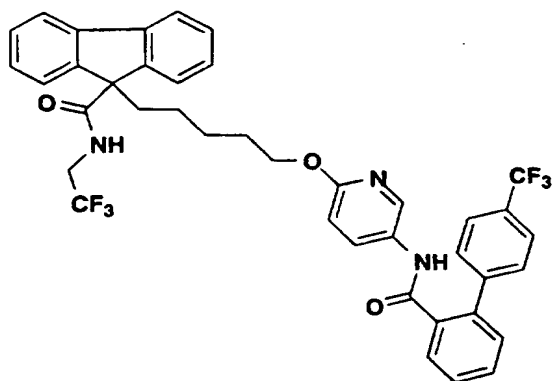
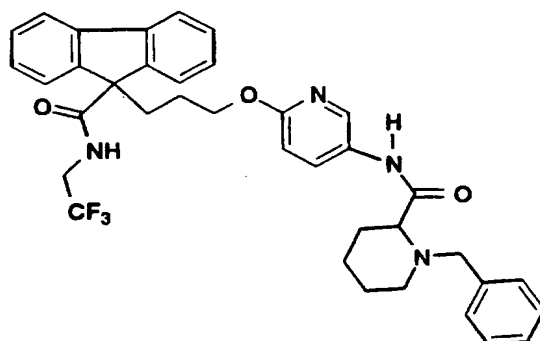
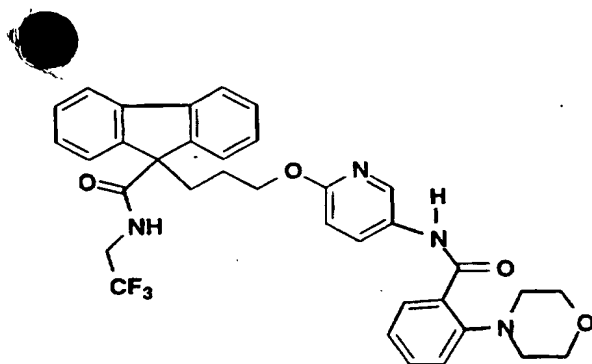
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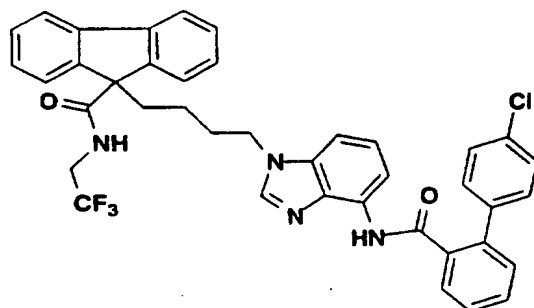
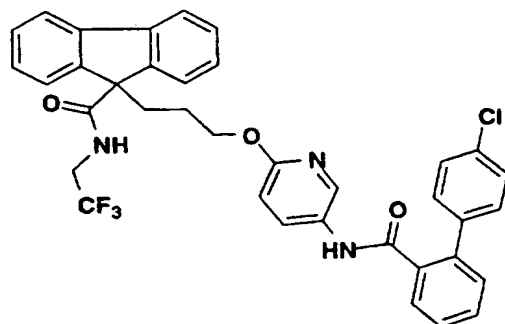
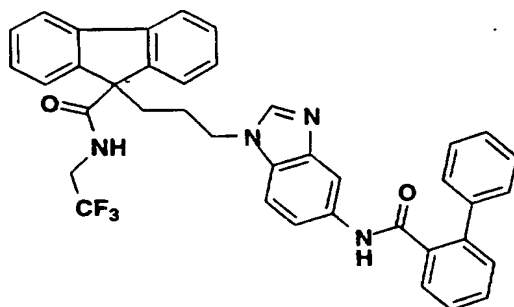


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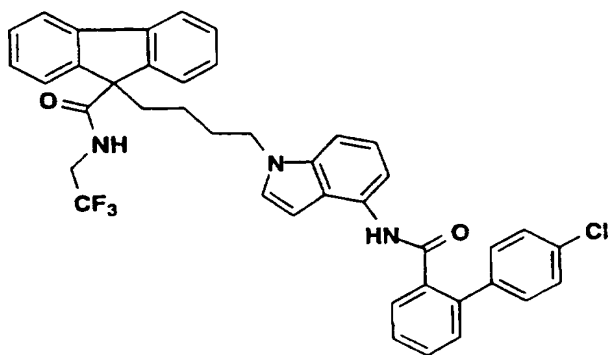


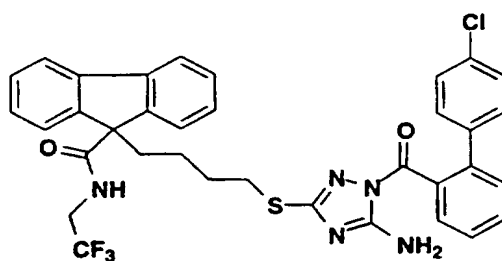
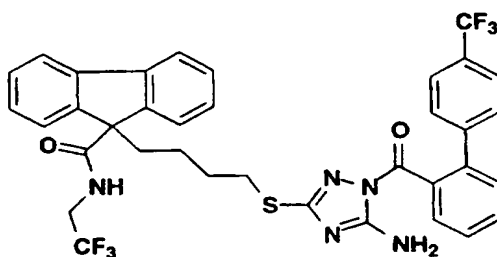
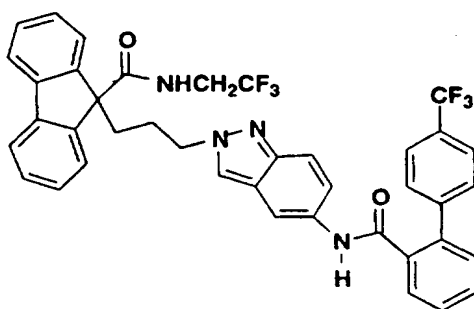
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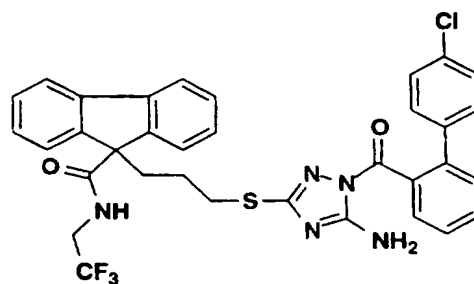
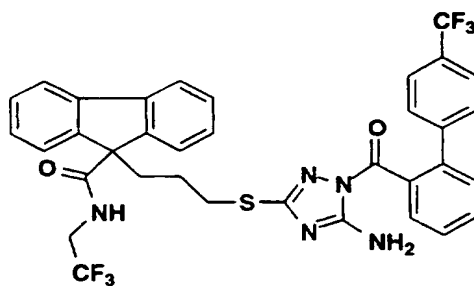


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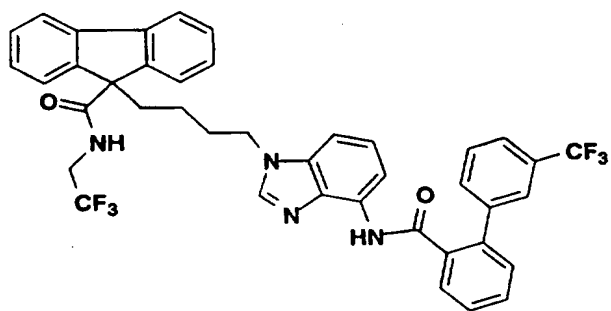
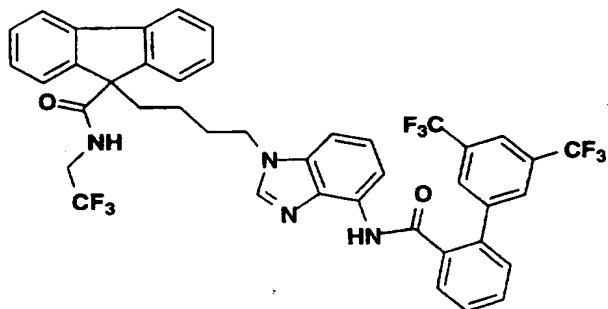
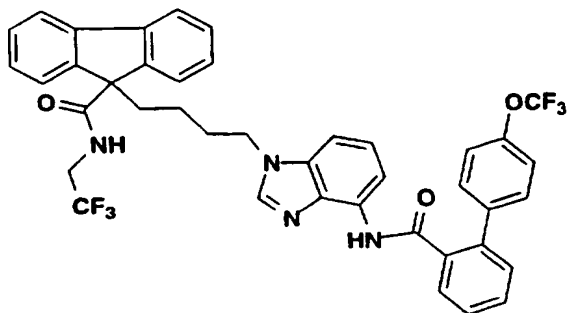
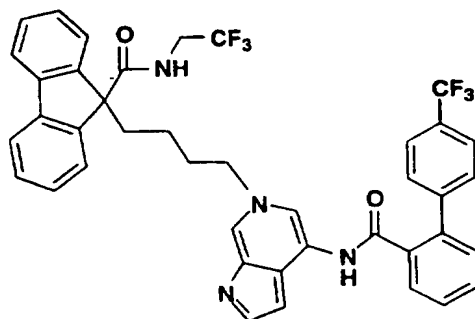




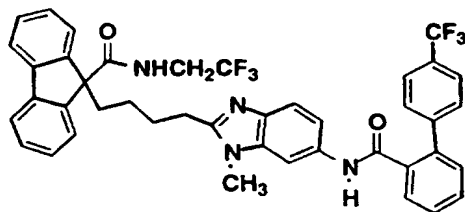
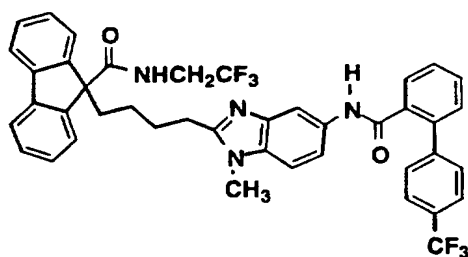
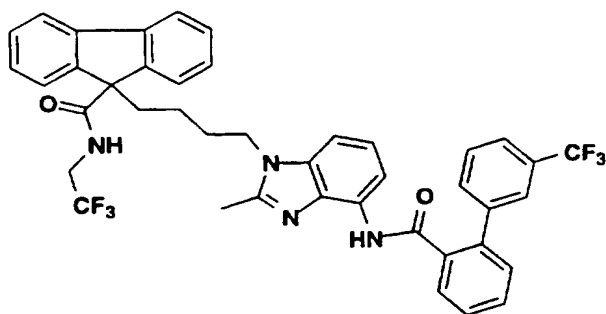
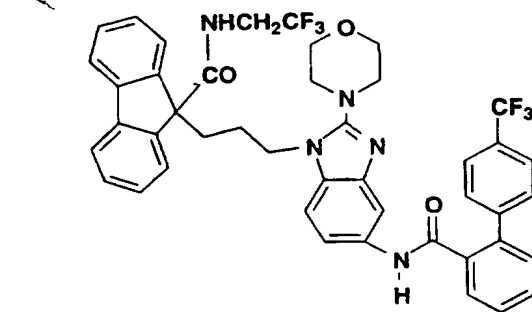
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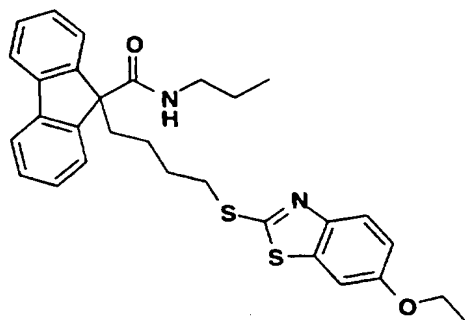
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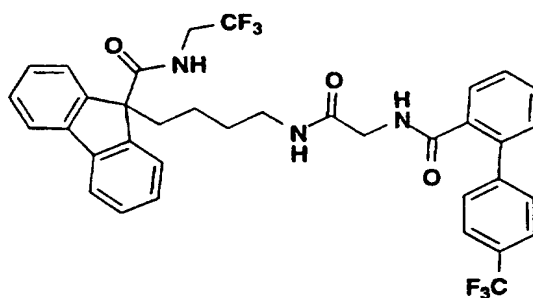
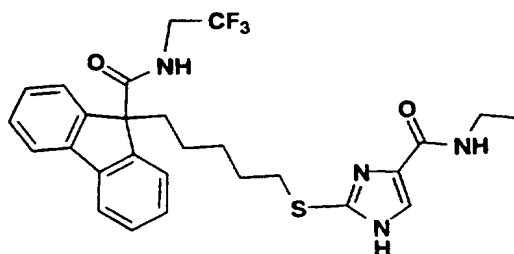
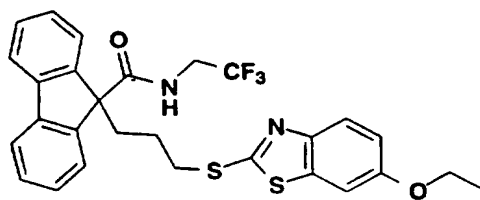


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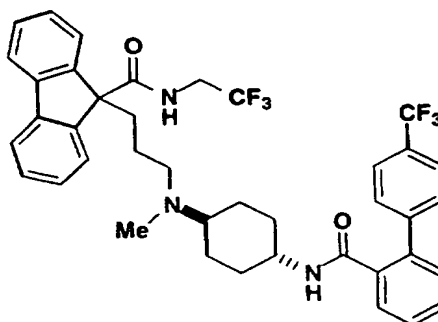
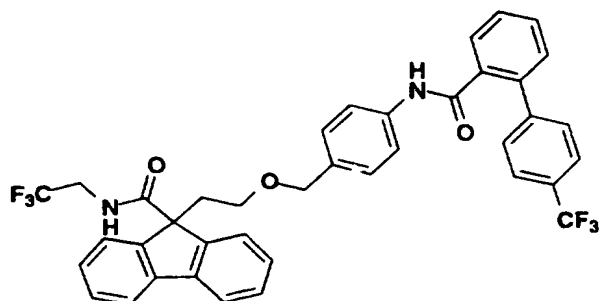


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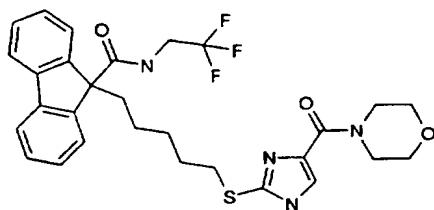
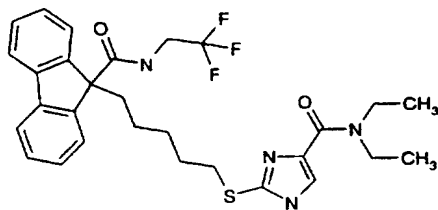
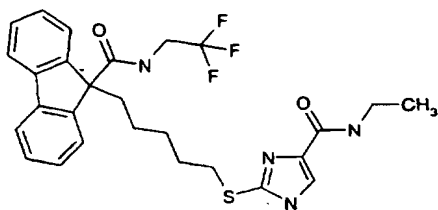




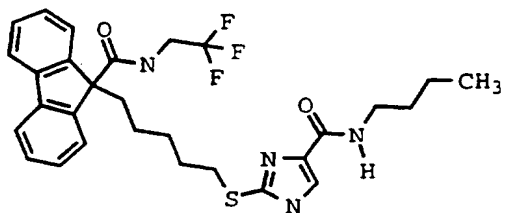
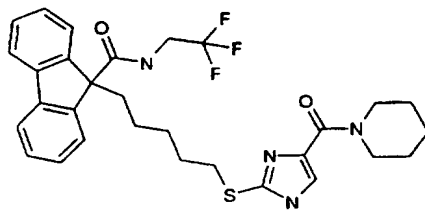
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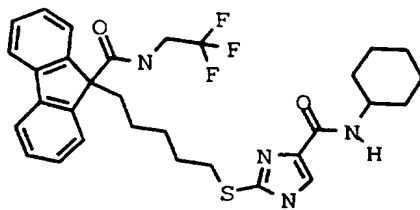
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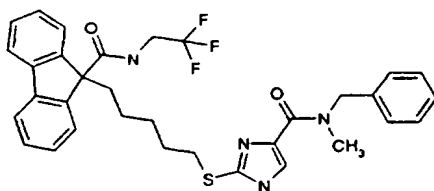
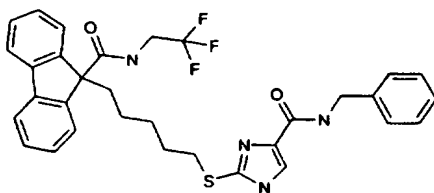
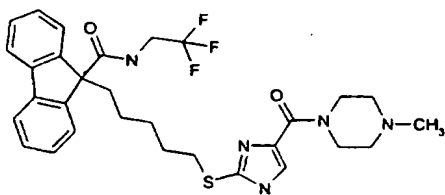


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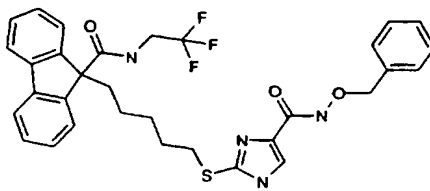
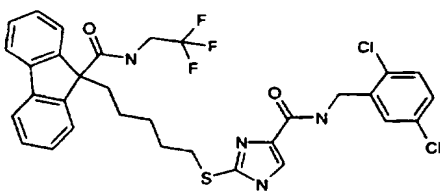


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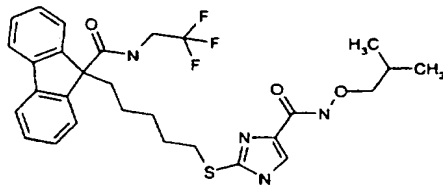
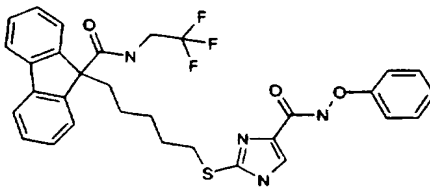


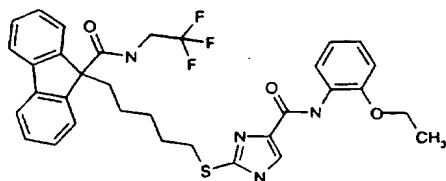
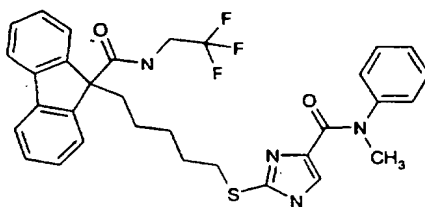


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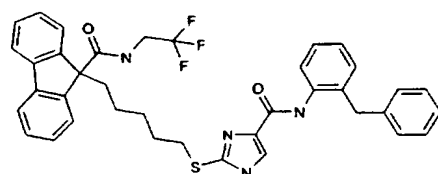
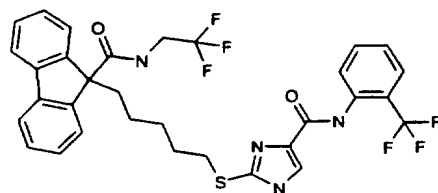
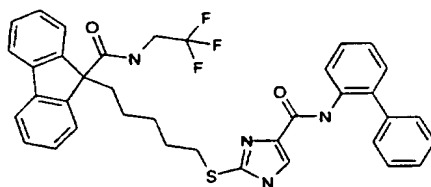


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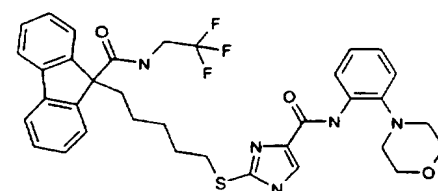
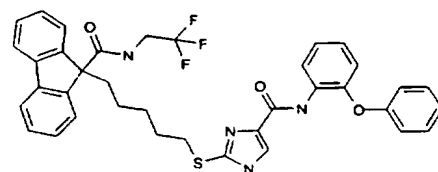


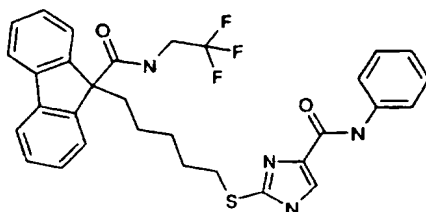
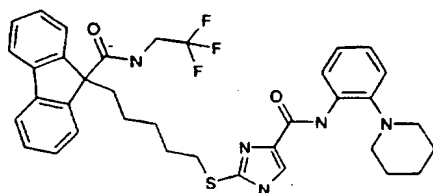


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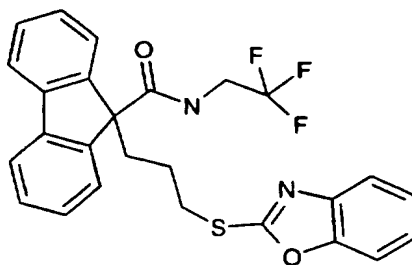
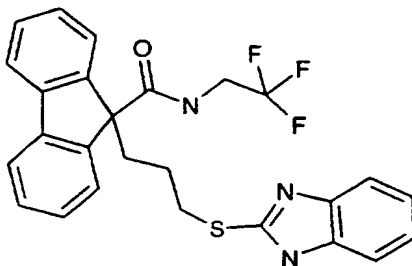


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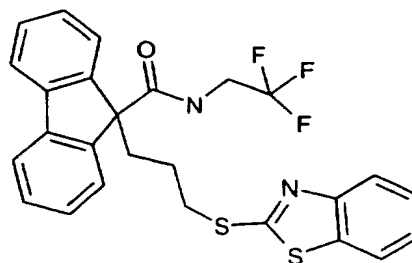


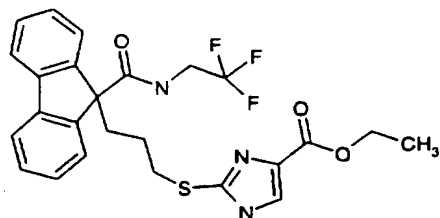
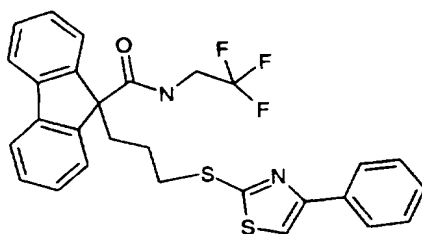
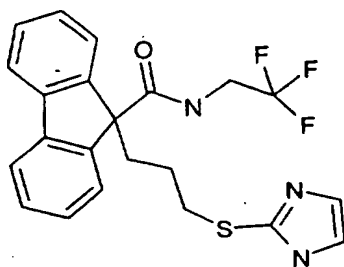


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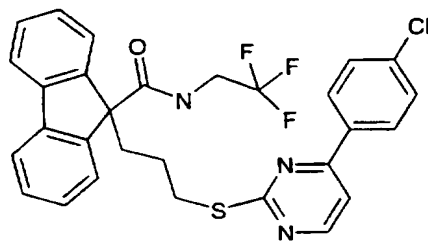
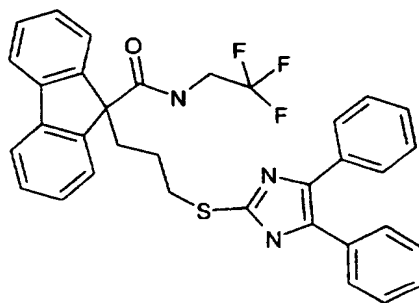


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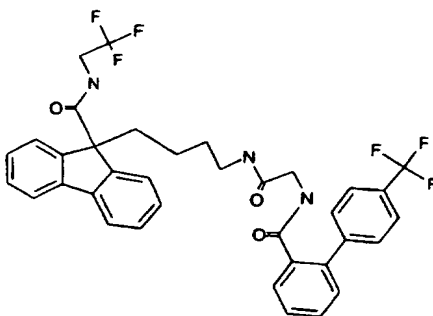
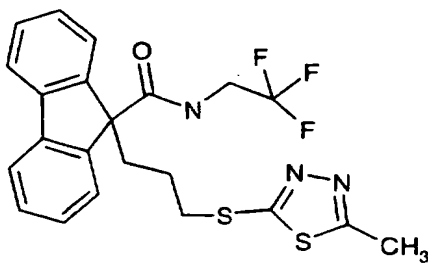
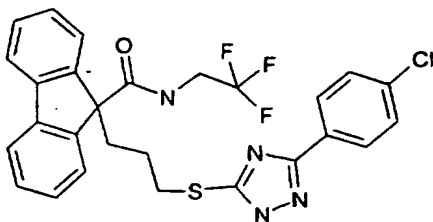




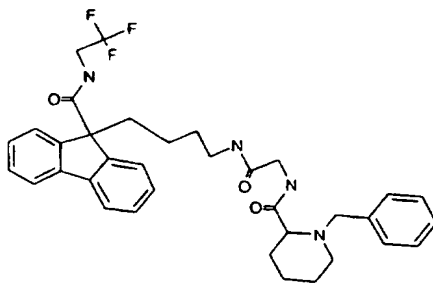
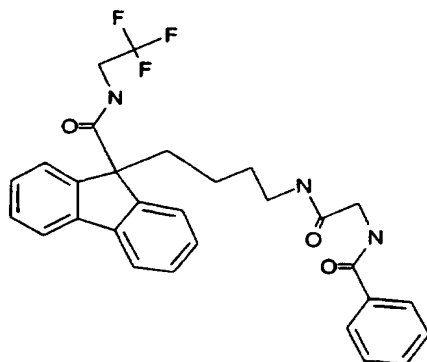
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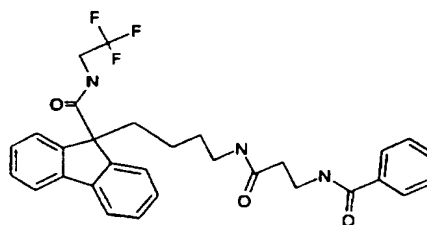
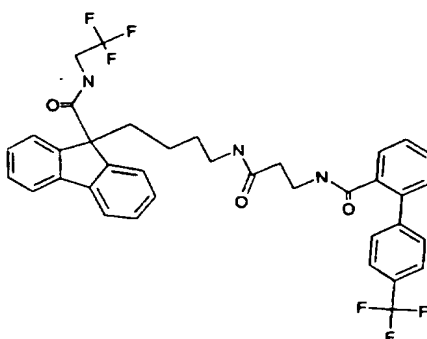
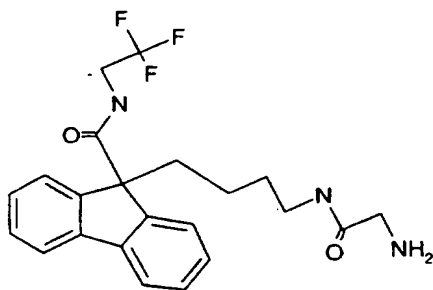


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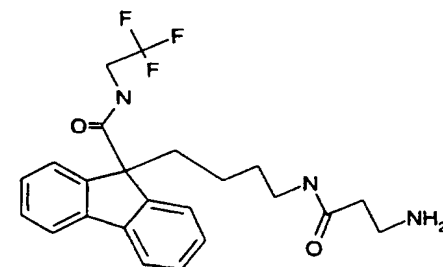
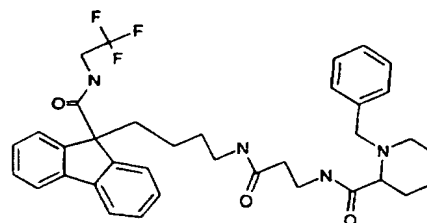


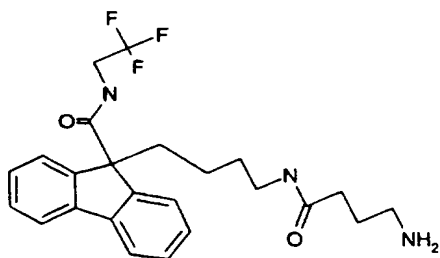
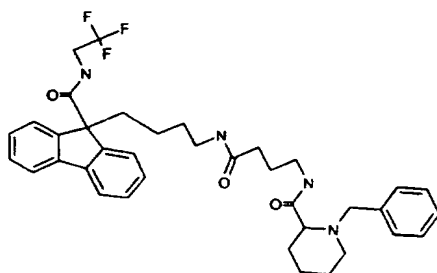
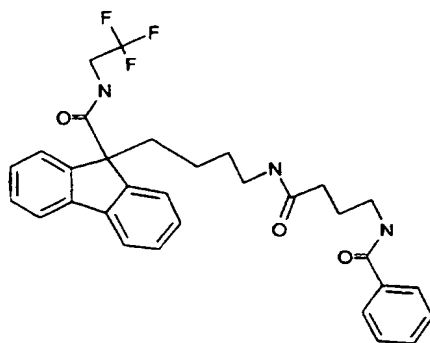
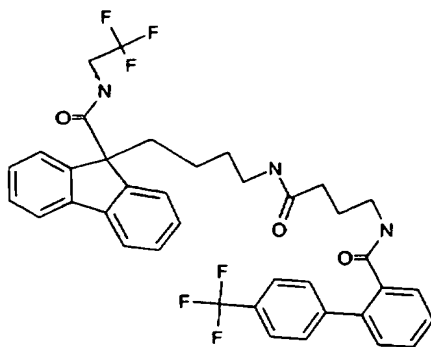
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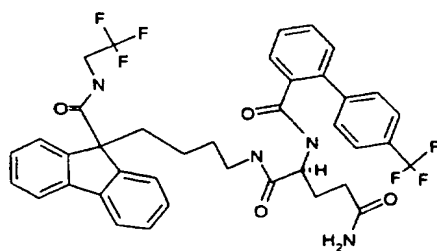


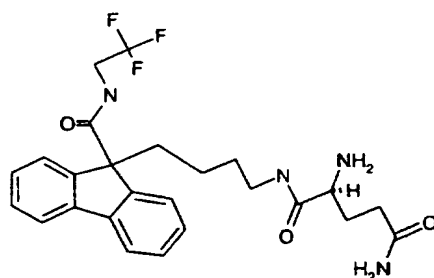
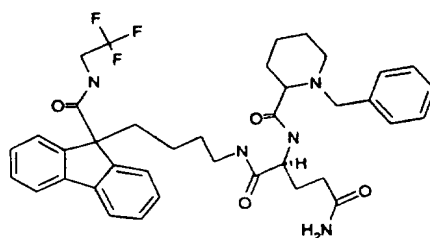
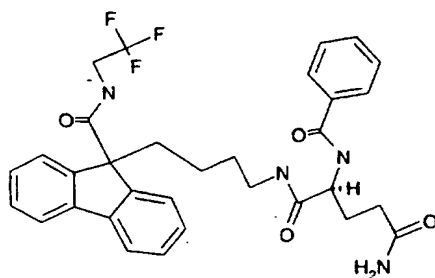
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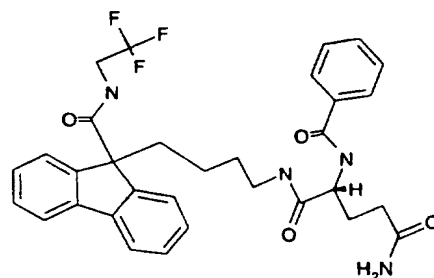
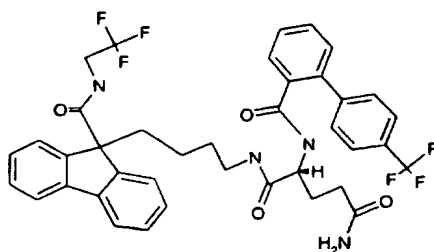


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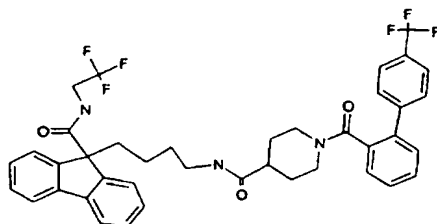
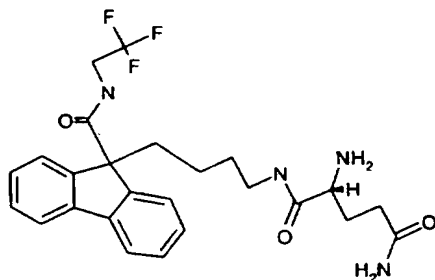
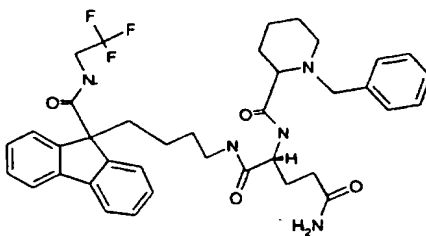




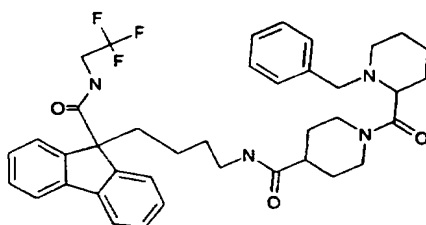
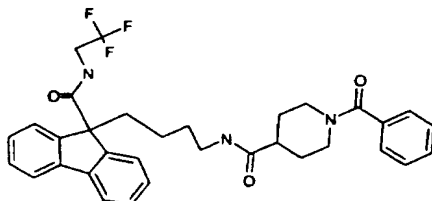
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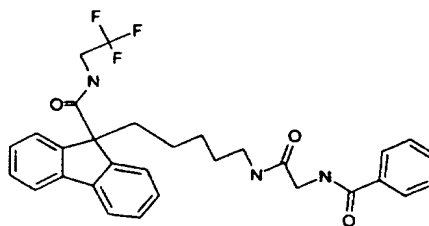
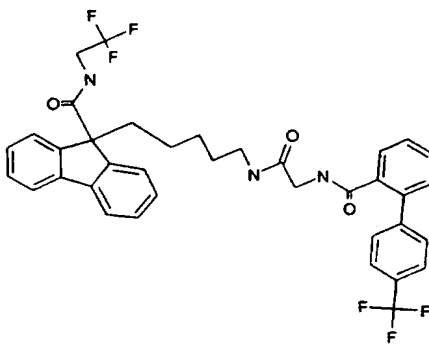
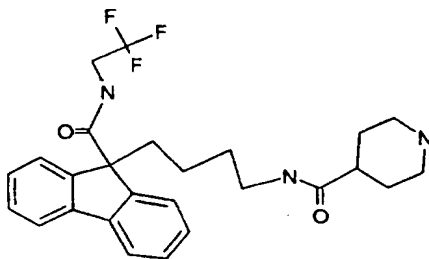
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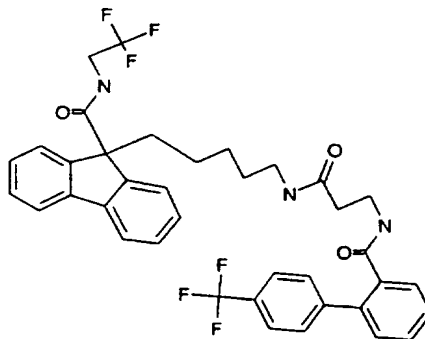
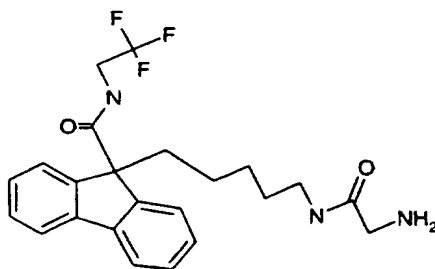
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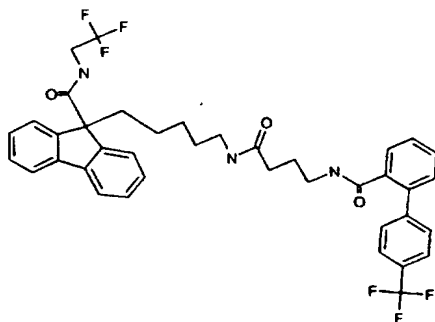
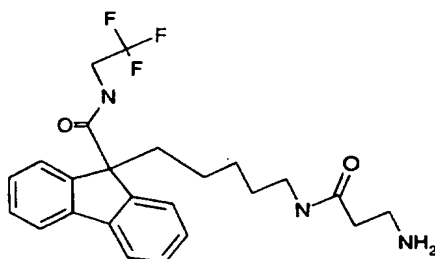
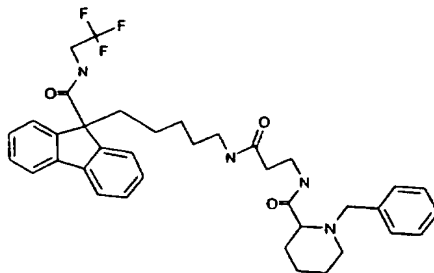
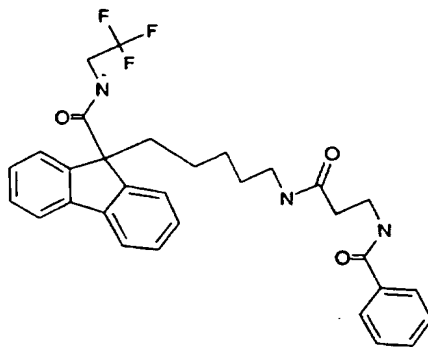


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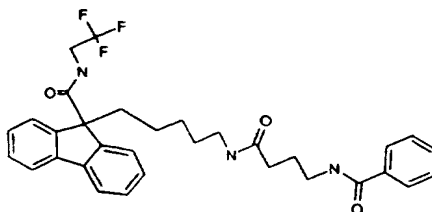


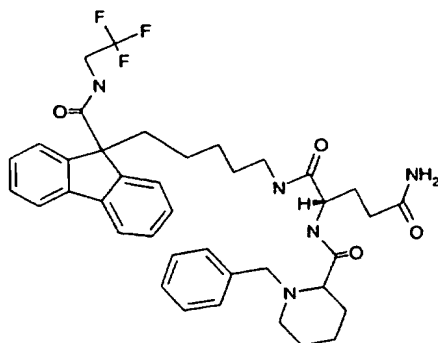
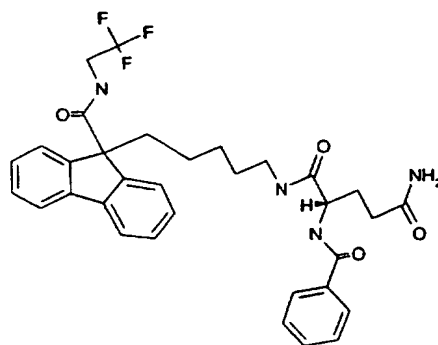
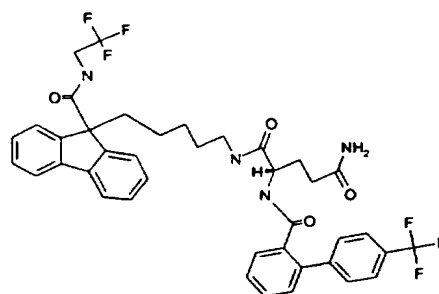
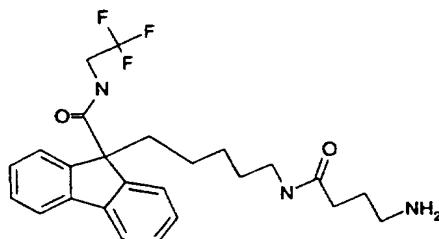
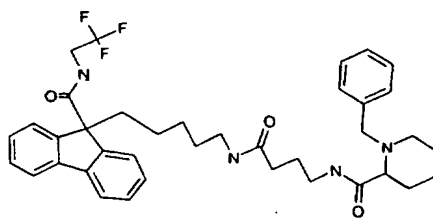
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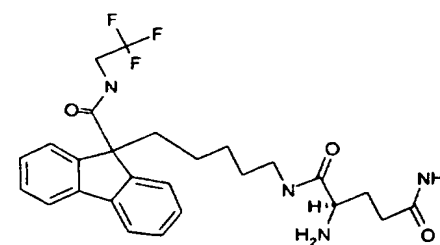
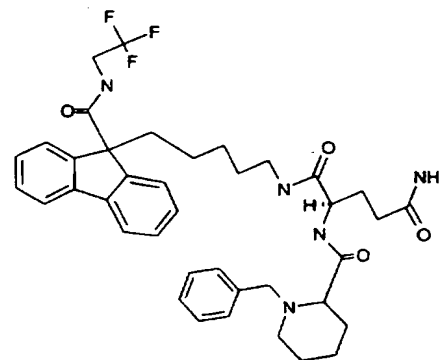
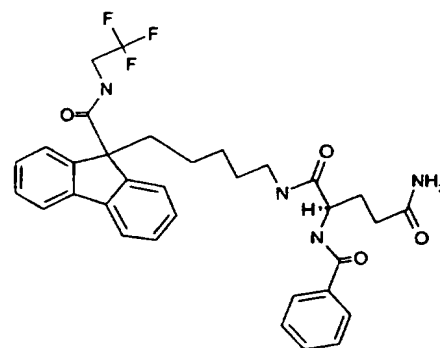
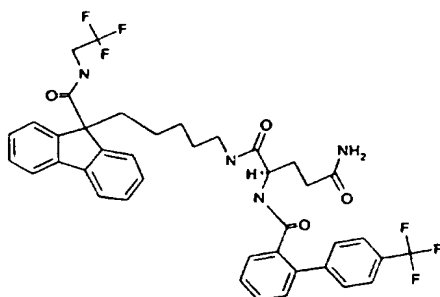
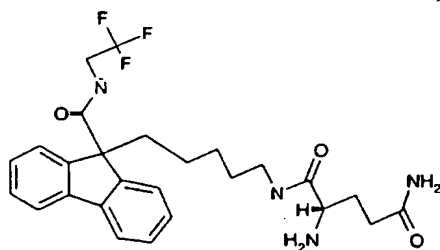


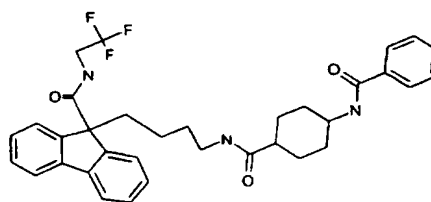
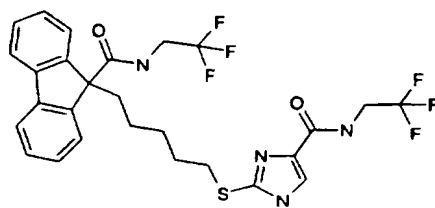
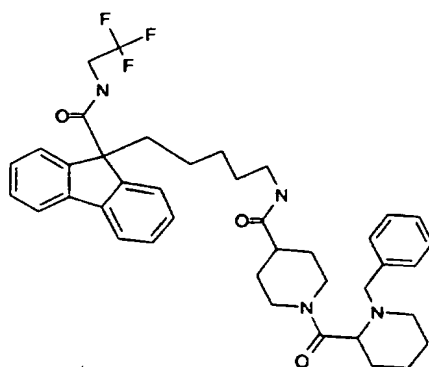
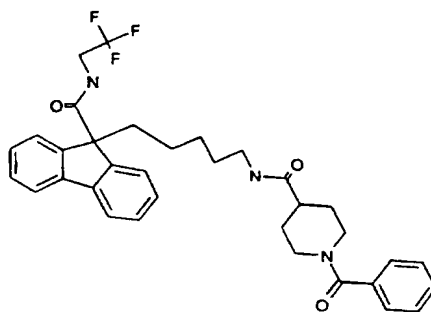
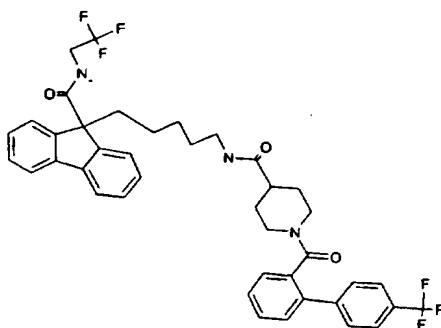


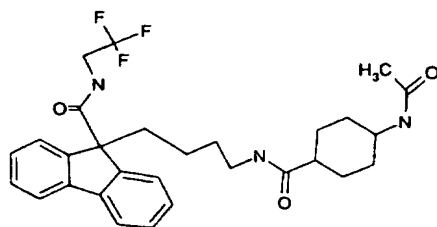
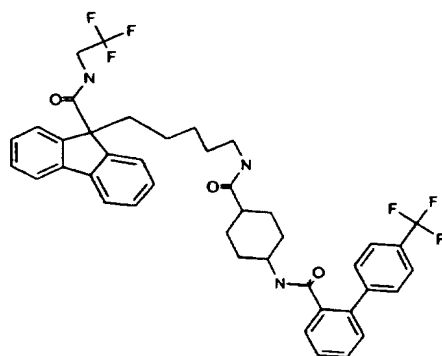
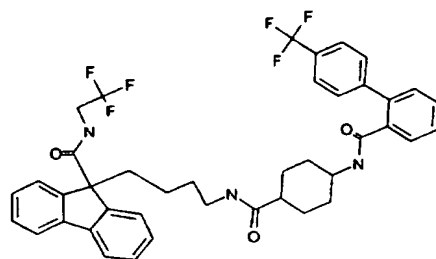
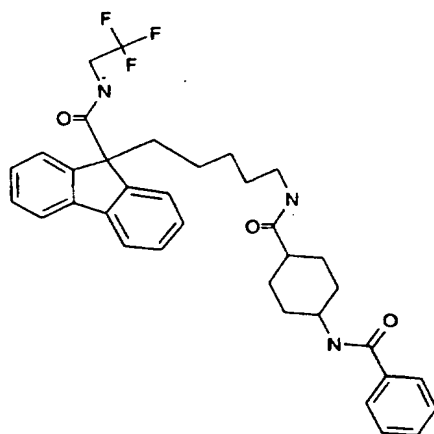
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/00587

A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

C07C 217/04; C07D 471/04, 471/10, 233/78, 401/08, 403/08; A61K 31/24, 31/445, 31/415, 31/44, 31/47, 31/495

A. CLASSIFICATION OF SUBJECT MATTER: US CL :

544/238, 294, 357, 405, 333; 546/86, 87, 15, 255, 256, 268, 279, 283, 284; 548/147, 216, 308, 411; 568/333

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

The compounds where one selects a variable from one of each of the following groups.

1. One of formulas I, IA or IB.
2. B equal to one of the seven fluorenyl-type structures.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The formulas defined for B and the formulas of I, IA and IB constitute distinct compounds not sharing a common core.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/00587

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark a Protest



The additional search fees were accompanied by the applicant's protest.



No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/00587

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/238, 294, 357, 405, 333; 546/86, 87, 15, 255, 256, 268, 279, 283, 284; 548/147, 216, 308, 411; 568/333

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
chemical abstracts formula search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,173,489 A (EARL et al.) 22 December 1992, see entire document.	1-26
A	US 4,277,495 A (LACEFIELD et al.) 07 July 1981, see entire document.	1-26
A	US 5,272,269 A (JENSEN et al.) 21 December 1993, see entire document.	1-26
A	US 4,864,028 A (YORK, JR.) 05 September 1989, see entire document.	1-26
A, P	WO 96/40640 A1 (PFIZER INC.) 19 December 1996, see entire document.	1-26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 29 MAY 1997	Date of mailing of the international search report 25 JUN 1997
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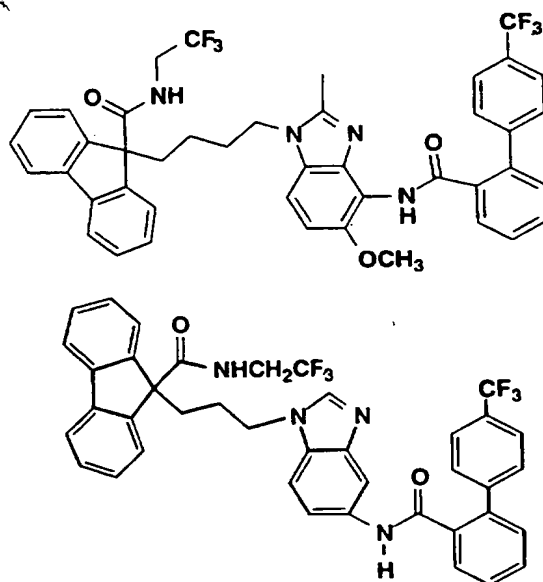
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Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

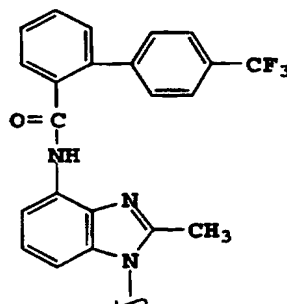
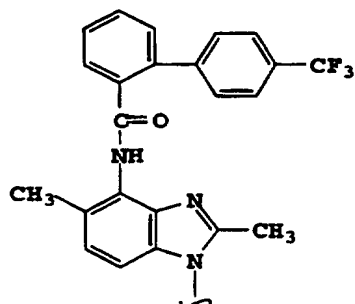
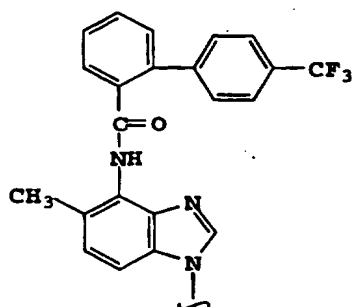
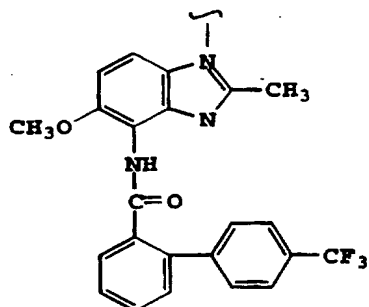
Authorized officer

JAMES H REAMER

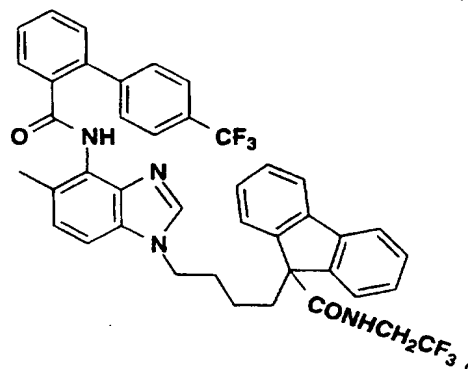
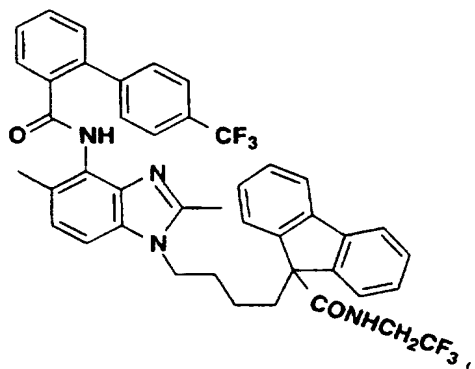
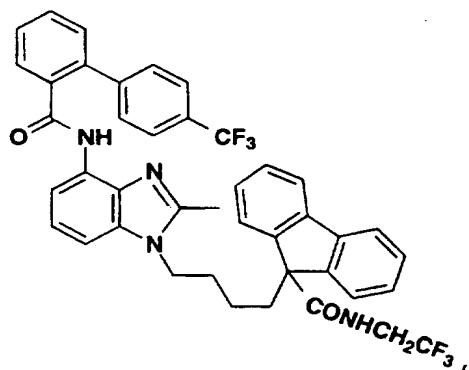
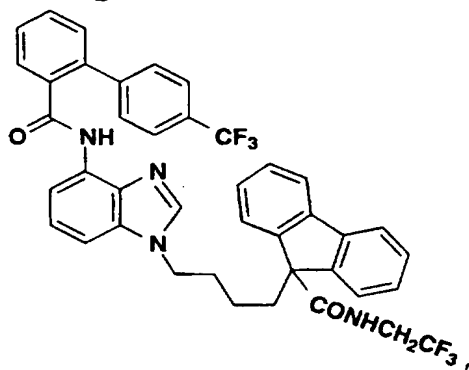
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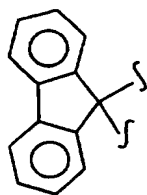


or a pharmaceutically acceptable salt thereof.



5 26. The compound as defined in Claim 23
having the structures





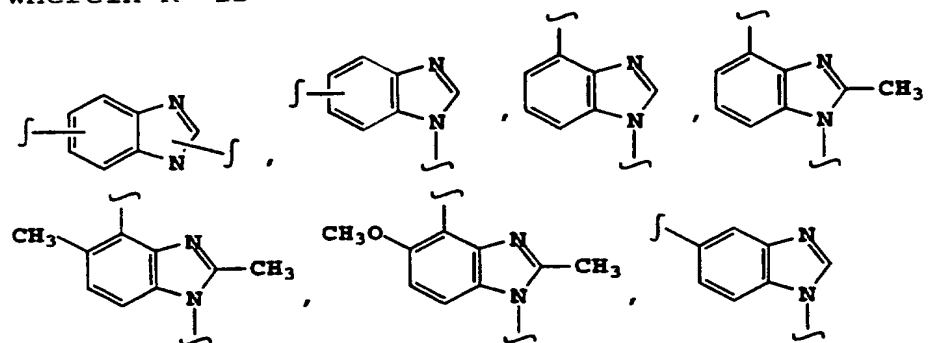
A is NH

L^2R^2 is CH_2CF_3

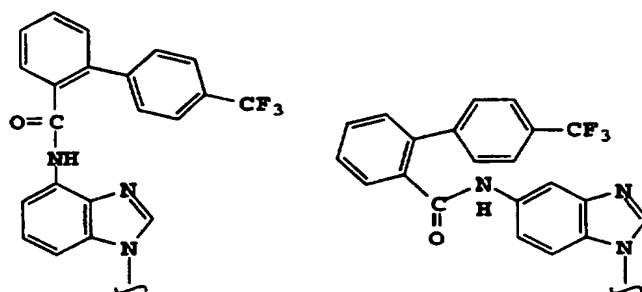
L^1 is $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$, and

- 5 R^1 is heteroaryl which is a 5-membered aromatic ring which includes 2 nitrogen atoms, which ring is fused to an aryl ring and is substituted on the aryl moiety.

24. The compound as defined in Claim 1
10 wherein R^1 is



25. The compound as defined in Claim 1
15 wherein R^1 is



R² is alkyl, polyfluoroalkyl, alkenyl, aryl, phenyl, heteroaryl, imidazolyl or pyridyl, wherein each of the above is optionally substituted;

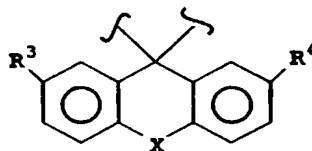
L¹ is a chain containing 1 to 5 atoms in a
5 linear chain;

L² is a bond or lower alkylene;

q is 0, 1 or 2.

22. The method as defined in Claim 16
where in the compound IB,

10 B is



X is a bond, oxygen or sulfur;

R³ and R⁴ are the same or different and are
H or F;

15 R¹ is aryl, phenyl, heteroaryl, imidazolyl, pyridyl, cyclohexyl, PO(R¹³)(R¹⁴), heteroarylthio, indolyl, benzimidazolyl, benzthiazole-2-thio, imidazole-2-thio, alkyl or alkenyl, 1,3-dioxan-2-yl, wherein each of the above is optionally
20 substituted;

R² is alkyl, polyfluoroalkyl, alkenyl, aryl, phenyl, heteroaryl, imidazolyl or pyridyl, wherein each of the above is optionally substituted;

L¹ is a chain containing 1 to 5 atoms in a
25 linear chain;

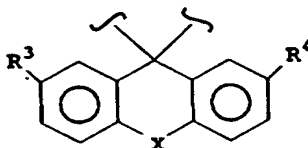
L² is a bond or lower alkylene;

R^x is H.

23. The compound as defined in Claim 1
having the formula



wherein B is



A is NH;

X is a bond, oxygen or sulfur;

R³ and R⁴ are the same or different and are

5 H or F;

R¹ is aryl, phenyl, heteroaryl, imidazolyl, pyridyl, cyclohexyl, PO(R¹³)(R¹⁴), heteroarylthio, indolyl, benzimidazolyl, benzthiazole-2-thio, imidazole-2-thio, alkyl or alkenyl, 1,3-dioxan-2-yl, wherein each of the above is optionally substituted;

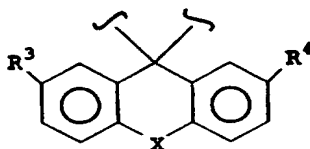
R² is alkyl, polyfluoroalkyl, alkenyl, aryl, phenyl, heteroaryl, imidazolyl or pyridyl, wherein each of the above is optionally substituted;

15 L¹ is a chain containing 1 to 5 atoms in a linear chain;

L² is a bond or lower alkylene.

21. The method as defined in Claim 16 where in the compound IA, B is

20



X is a bond, oxygen or sulfur;

R³ and R⁴ are the same or different and are

H or F;

25 R¹ is aryl, phenyl, heteroaryl, imidazolyl, pyridyl, cyclohexyl, PO(R¹³)(R¹⁴), heteroarylthio, indolyl, benzimidazolyl, benzthiazole-2-thio, imidazole-2-thio, alkyl or alkenyl, 1,3-dioxan-2-yl, wherein each of the above is optionally substituted;

30

R^7 and R^8 are the same or different and are independently H, alkyl, aryl, halogen, $-O-R^{12}$, or R^7 and R^8 together can be oxygen to form a ketone;

5 R^9 , R^{10} , $R^{9'}$ and $R^{10'}$ are the same or different and are independently H, lower alkyl, aryl or $-O-R^{11}$;

10 R^9 , and $R^{10''}$ are the same or different and are independently H, lower alkyl, aryl, halogen or $-O-R^{11}$;

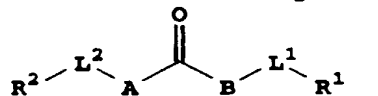
R^{11} is alkyl or aryl;

R^{12} is H, alkyl or aryl;

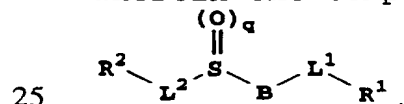
with respect to IA and IB, R^2L^2 cannot have an O or N atom directly attached to $S=(O)_q$ or $CR^x(OH)$, and for IA, R^2 , L^2 cannot be H; and

with respect to I, IA and IB, where R^1 or R^2 is cycloheteroalkyl, R^1 or R^2 is exclusive of 1-piperidinyl, 1-pyrrolidinyl, 1-azetidiny or 1-(2-oxo-pyrrolidinyl).

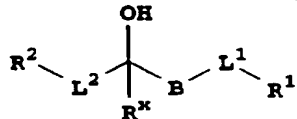
20 17. The method as defined in Claim 16 wherein the compound has the structure



18. The method as defined in Claim 16 wherein the compound has the structure



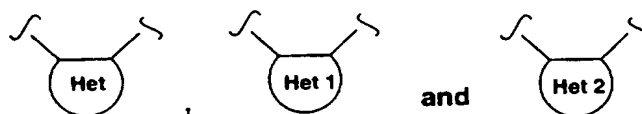
19. The method as defined in Claim 16 wherein the compound has the structure



20. The method as defined in Claim 16
30 where in the compound I, B is

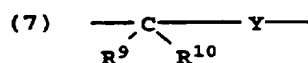
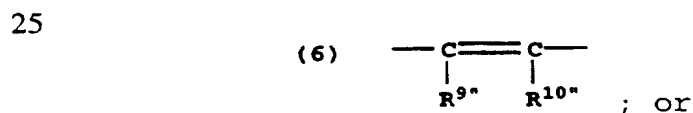
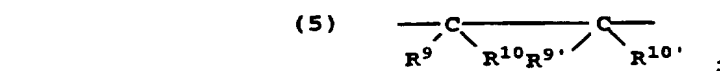
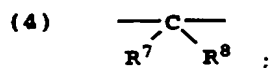
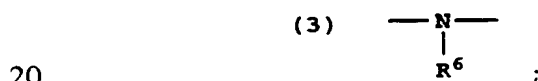
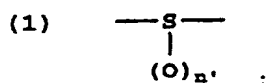
carbonylamino, wherein Ar is aryl or heteroaryl and Ar may optionally include 1, 2 or 3 additional rings fused to Ar;

- 5 R^{3a} and R^{3b} are the same or different and are independently any of the R^3 groups except hydroxy, nitro, amino or thio;



- 10 are the same or different and independently represent a 5 or 6 membered heteroaryl ring which contains 1, 2, 3 or 4 heteroatoms in the ring which are independently N, S or O; and including N-oxides;

- 15 X is a bond, or is one of the following groups:



wherein

- 30 Y is O, N- R^6 or S;
 n' is 0, 1 or 2;
 R^6 is H, lower alkyl, aryl, $-\text{C}(\text{O})-\text{R}^{11}$ or $-\text{C}(\text{O})-\text{O}-\text{R}^{11}$;

where J is: CHR^{23} , $\begin{array}{c} \text{---C---} \\ || \\ \text{O} \end{array}$, $\begin{array}{c} \text{---CH---CH---} \\ | \quad | \\ \text{R}^{24} \quad \text{R}^{25} \end{array}$ or $\begin{array}{c} \text{---C=C---} \\ | \quad | \\ \text{R}^{24} \quad \text{R}^{25} \end{array}$;

R^{23} , R^{24} and R^{25} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

5 R^{20} , R^{21} , R^{22} are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl; and these substituents may
10 either be directly attached to R^1 , or attached via an alkylene at an open position;

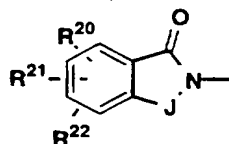
R^2 is independently any of the groups set out for R^1 , H, polyhaloalkyl or cycloheteroalkyl, and may be optionally substituted with one to four
15 of any of the groups defined for R^3 or substituents defined for R^1 ;

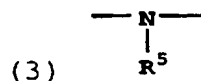
L^1 is a linking group containing up from 1 to 10 carbons in a linear chain including alkylene, alkenylene or alkynylene, which may contain, within
20 the linking chain any of the following: one or two alkenes, one or two alkynes, an oxygen, an amino group, an oxo group, and may be substituted with one to five alkyl or halo groups;

L^2 may be the same or different from L^1 and
25 may independently be any of the L^1 groups set out above or a single bond;

R^3 , $\text{R}^{3'}$, R^4 and $\text{R}^{4'}$ may be the same or different and are independently selected from H, halogen, CF_3 , haloalkyl, hydroxy, alkoxy, alkyl,
30 aryl, alkenyl, alkenyloxy, alkynyl, alkynyloxy, alkanoyl, nitro, amino, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, cycloheteroalkyl, cycloheteroalkylalkyl, cyano, Ar,
35 Ar-alkyl, ArO, Ar-amino, Ar-thio, Ar-sulfinyl, Ar-sulfonyl, Ar-carbonyl, Ar-carbonyloxy or Ar-

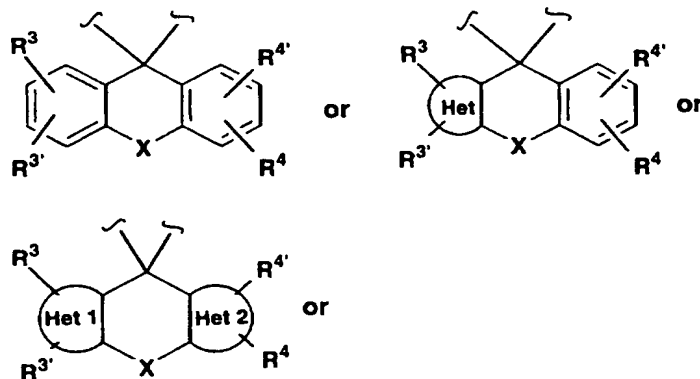
- aryl, arylalkyl, arylamino, aryloxy, heteroaryl, heteroarylamino, heteroaryloxy, arylsulfonylamino, heteroarylsulfonylamino, arylthio, arylsulfinyl, arylsulfonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, cycloheteroalkyl heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, -PO(R¹³)(R¹⁴) (where R¹³ and R¹⁴ are independently alkyl, aryl, alkoxy or aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy or cycloheteroalkylalkoxy); aminocarbonyl (where the amino may optionally be substituted with one or two aryl, alkyl or heteroaryl groups); cyano, 1,1-(alkoxyl or aryloxy)₂alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring connected to L¹ (or L² in the case of R²) at the 2-position); 1,3-dioxane or 1,3-dioxolane connected to L¹ (or L² in the case of R²) at the 4-position; the R¹ group may optionally be substituted with 1, 2, 3 or 4 substituents, which can be any of the R³ or R¹ groups, or alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxy carbonylamino, aryloxy carbonylamino, heteroaryloxy carbonylamino, uriedo (where the uriedo nitrogens may optionally be substituted with alkyl, aryl or heteroaryl), heterocyclylcarbonylamino (where the heterocycle is connected to the carbonyl group via a nitrogen or carbon atom), alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,





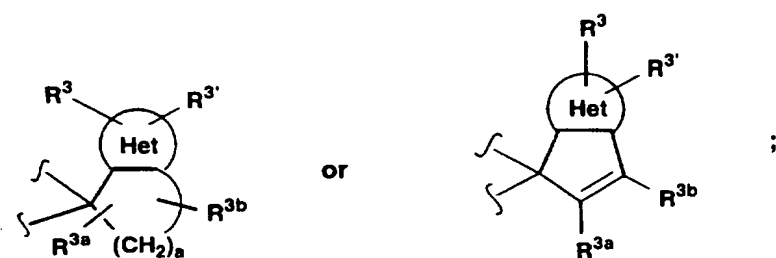
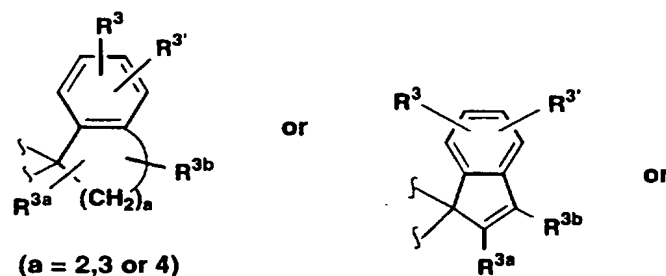
where R^5 is H or lower alkyl, or R^5 together with R^2 forms a carbocyclic or heterocyclic ring system containing 4 to 8 members in the ring;

5 B is a fluorenyl-type group of the structure



10

B is an indenyl-type group of the structure

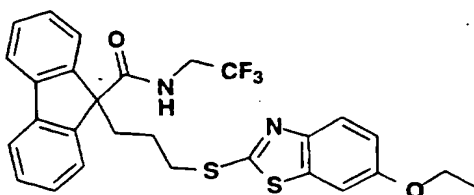


15

R^x is H, alkyl or aryl;

R^1 is H, alkyl, alkenyl, alkynyl, alkoxy, (alkyl or aryl)₃Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, substituted alkylamino, substituted arylalkylamino,

20



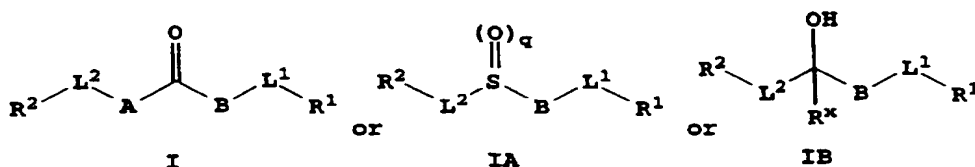
or

pharmaceutically acceptable salts thereof;
esters thereof or prodrug esters thereof.

5 14. The compound as defined in Claim 10
wherein A is NH and R²L² is CF₃CH₂.

15. A method for preventing, inhibiting or treating atherosclerosis, pancreatitis, noninsulin dependent diabetes, or obesity in a mammalian species, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

16. A method of lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hyperglycemia and/or hypertriglyceridemia, and/or preventing, inhibiting or treating atherosclerosis, pancreatitis, noninsulin dependent diabetes, or obesity in a mammalian species, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound having the structure

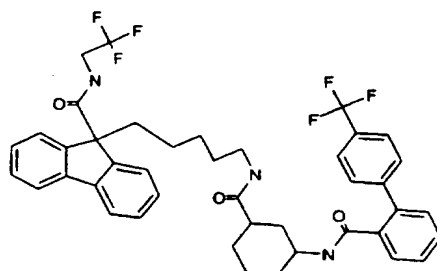
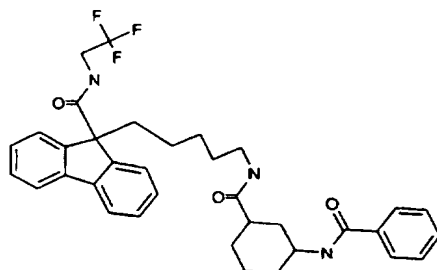
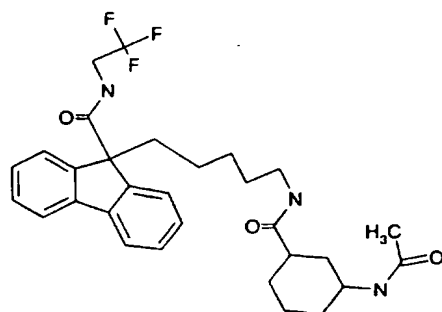
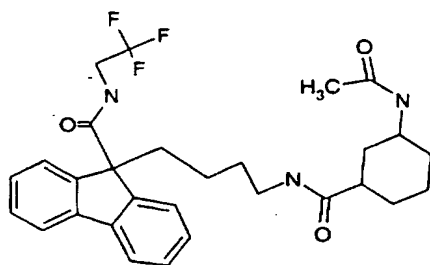


including pharmaceutically acceptable salts thereof, N-oxides thereof,

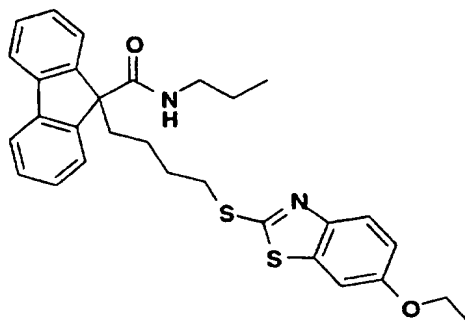
wherein q is 0, 1 or 2;

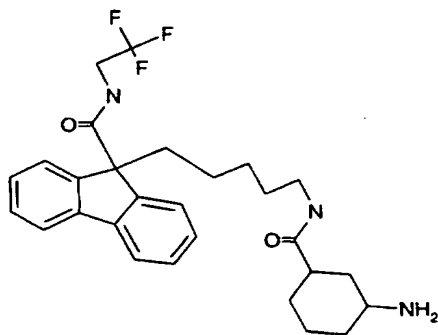
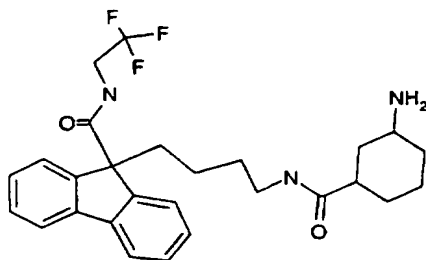
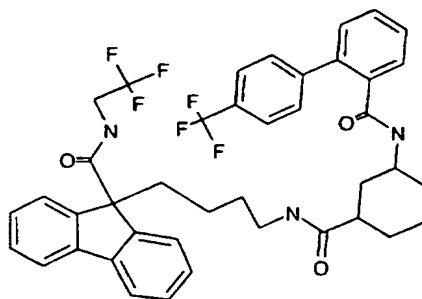
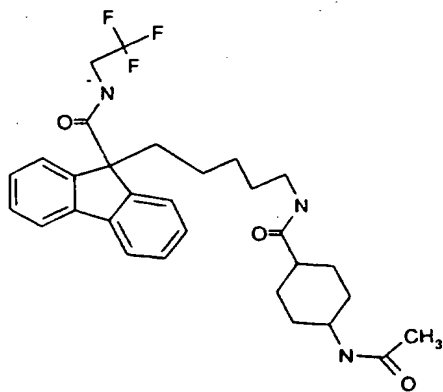
A is (1) a bond;

30 (2) -0-; or



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